PXT864 Overview

January 2020

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Alzheimer's Disease

CHARACTERISTICS / SYMPTOMS	Irreversible, progressive neurodegeneration leading to a state of dementia
POPULATION	1 in 8 people 65+ suffer from Alzheimer's disease >130 million worldwide cases expected by 2050 unless effective treatments discovered >20 million expected in China by 2050
TREATMENT OPTIONS	Poorly efficient on symptoms with frequent side effects and tolerability issues • **Cholinesterase inhibitor (essentially donepezil)** • **NMDA receptor antagonist (memantine)**
OUTCOME	Any better symptomatic relief and/or disease-modifying effects would be a success
CAUSE	Cause not entirely known, though characterized by accumulation of amyloid-beta (Aβ) and NFT in the brain
PXT864 BARRIERS TO ENTRY	Robust IP including composition of matter until at least 2032

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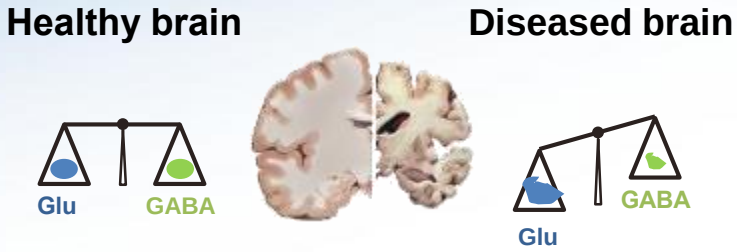
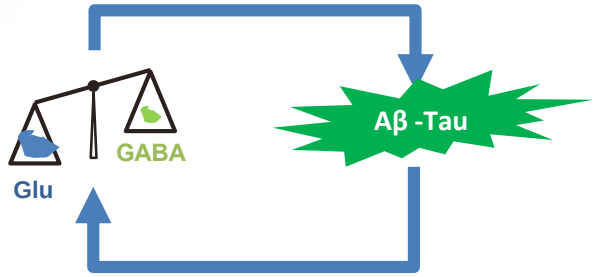
New Mechanism of Action:
Correcting chemical imbalance in the diseased brain

Disease at-a-glance



Glu: Glutamate

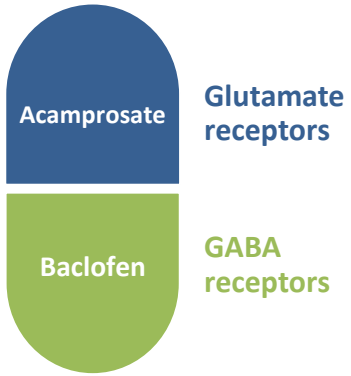
Vicious circle occurring in AD brain

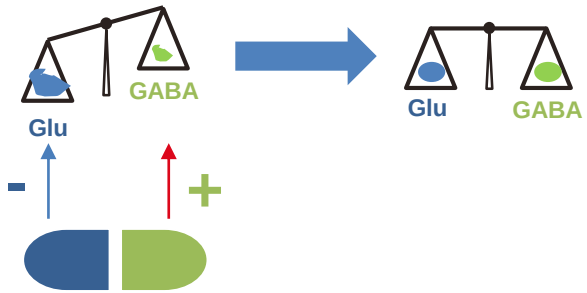


Upstream of **Aβ -Tau**
imbalanced cells overproduce each

E/I i.e. GLU excitation / GABA inhibition

PXT864 to break the vicious circle





"Therapeutics that correct the E/I imbalance in early AD may prevent neuronal dysfunction, cell loss and cognitive impairments associated with later stages of the disease" **Busche and Konnerth 2016**

(Govindpani 2017;; Talantova 2013)

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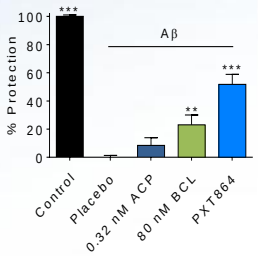
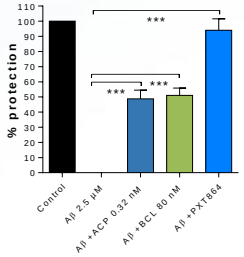
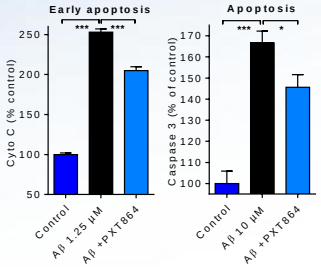
PXT864 Multitropic Activity *in vitro*

Protects neurons

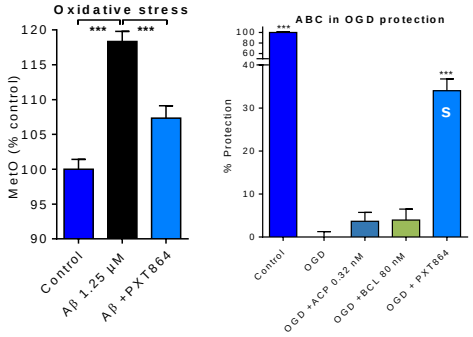




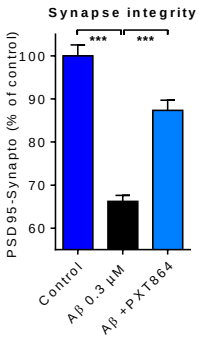
Protects against apoptosis



Prevents oxidative stress



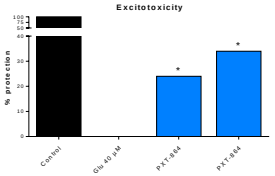
Preserve Synapses



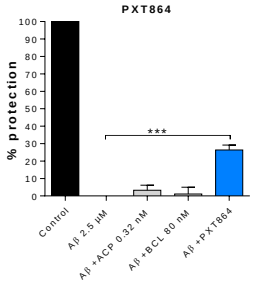
Baclofen

Acamprosate

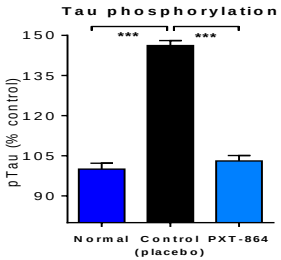
Prevents excitotoxicity



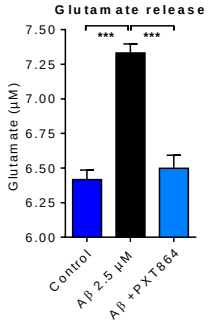
Protects vessels



Reduces Phospho tau



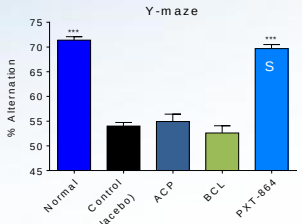
Decreases glutamate level

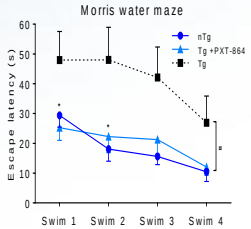


(Chumakov *et al.*, 2015)

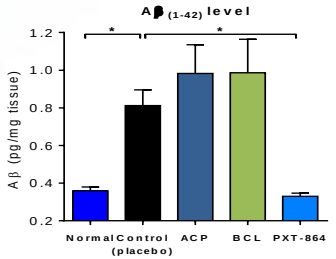
PXT864 Multitropic Efficacy *in vivo*

Alleviates cognitive deficits





Reduces Aβ levels



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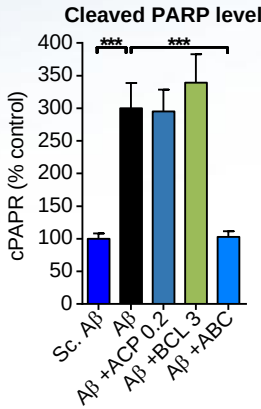

Baclofen

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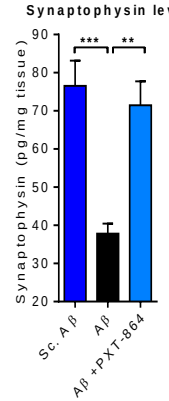
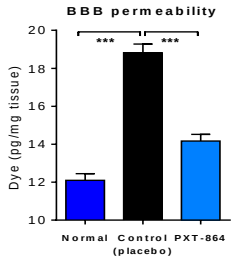
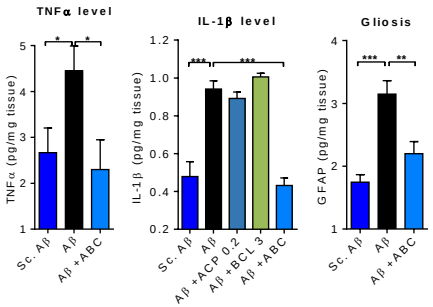
Preserve Synapses



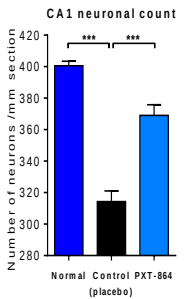
Protects the BBB



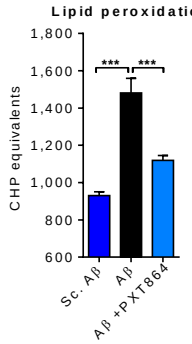
Decreases inflammation



Protects neurons



Prevents oxidative stress



(Chumakov et al., 2015)

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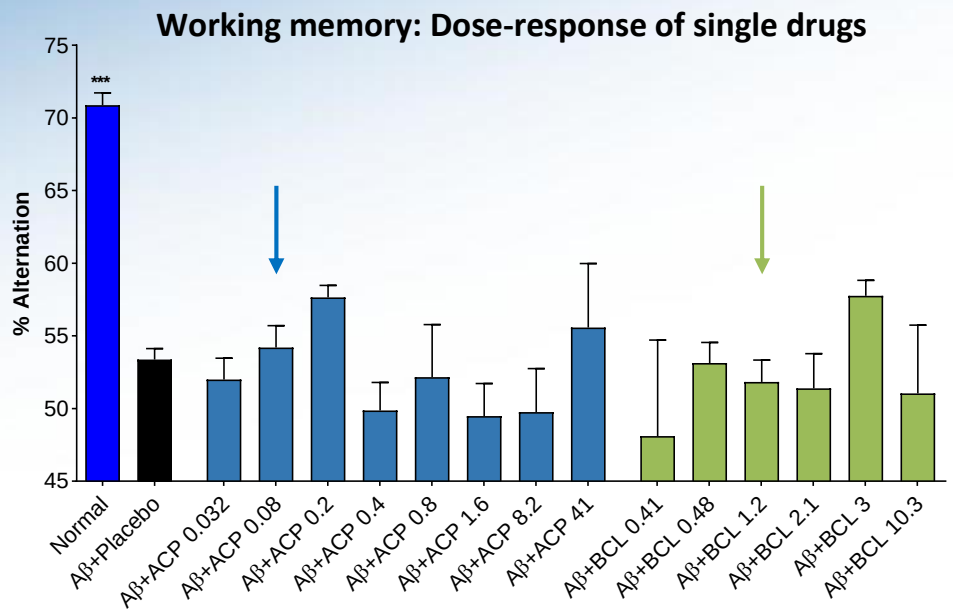
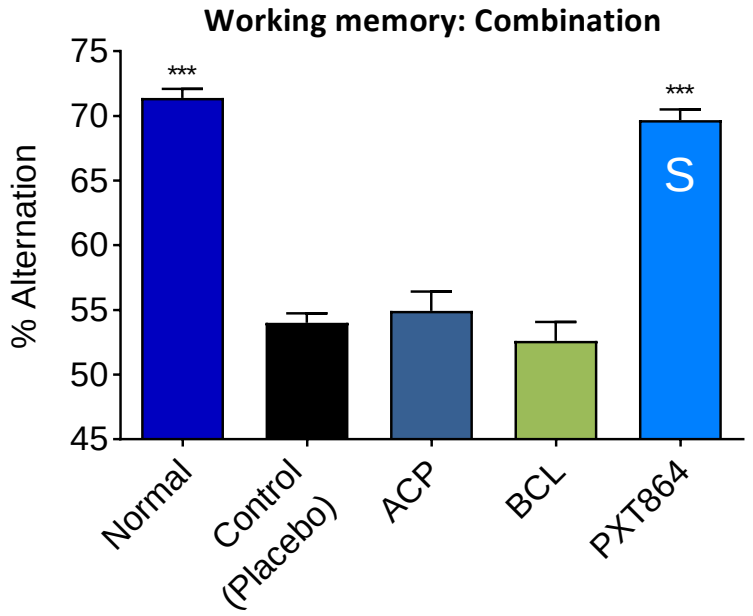
PXT864 is Efficacious Synergistically in AD Animals





(Chumakov 2015)

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PLEODIAL: Exploratory Phase 2a Trial Design

- 45 mild naïve AD patients treated by 3 doses:
- Clinically diagnosed but low mean Log Abeta 42/40
- 7 centers in France
- Assessed at 0,3,6,9 months
- 9 clinical endpoints, open label, single blind

(mg)	Acamprosate	Baclofen
Dose 1	0,8	12
Dose 2	2	30
Dose 3	40	24

Functions assessed by each endpoint

	Memory	Orientation	Language	Attention	Visuospatial	Executive function	speed	Daily activity	Social interaction
Adas Cog	■	■	■	■	■	■			
CDRSB	■	■		■		■		■	■
IADL		■			■	■		■	
TMT A			■	■	■	■	■		
TMT B			■	■	■	■	■		
ZAZZO				■	■	■	■		
Apathy Inventory			■					■	■
DSST				■	■	■	■		
ISAAC	■		■	■		■	■		

- Biomarker: Plasma $A\beta_{42/40}$ assessed by Quanterix

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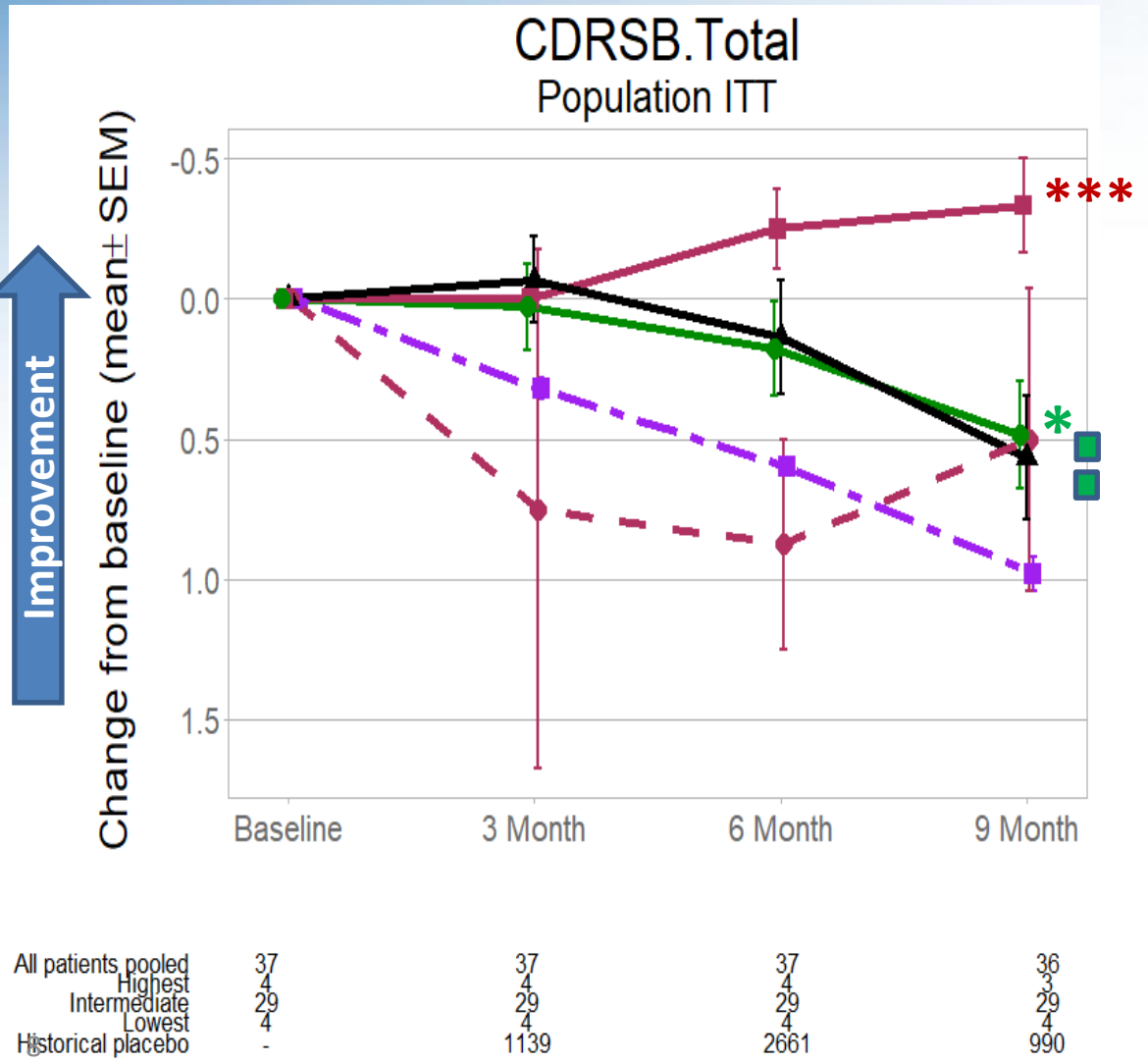
PXT864 on CDR-SB

Analysing Individual Plasma Drug Exposure Response Rather Than Ingested Dose Response

A Higher Dose Could Rapidly Generate Partial Recovery Rather Than Less Decline With No Safety Concerns



All patients pooled
Highest drug exposure
Intermediate drug exposure
Lowest drug exposure
Historical placebo

	Acamprosate	Baclofen
Approved dose	**2000 mg**	**80 mg**
Ingested dose 3	**40 mg**	**24 mg**
Next dose to be tested	**400 mg**	**24 mg**

Biogen ENGAGE : 9 months high dose Aducanumab: **~ 0,5 pts** decline / 116 patients
Biogen EMERGE : 9 months high dose Aducanumab: **~ 0,7 pts** decline / 146 patients

Both analyses with patients with sufficient exposure
(increasing dose limited by safety concerns)

*** p = 3e-13 Highest drug exposure versus historical placebo

* p = 0.013 All patients versus historical placebo

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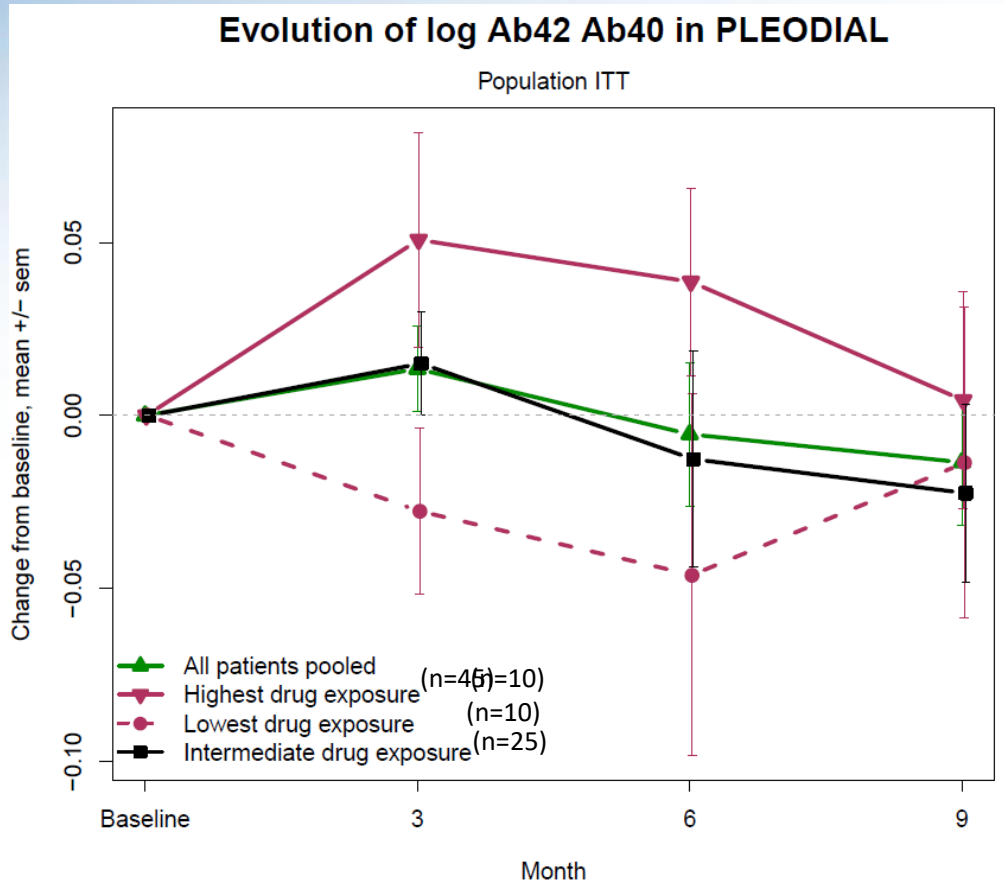
Plasma $A\beta_{42/40}$

Analysing Individual Plasma Drug Exposure Response Rather Than Ingested Dose Response Improvement At 3 And 6 Months But A Higher Dose Could Rapidly Generate Sustained Effect

Improvement



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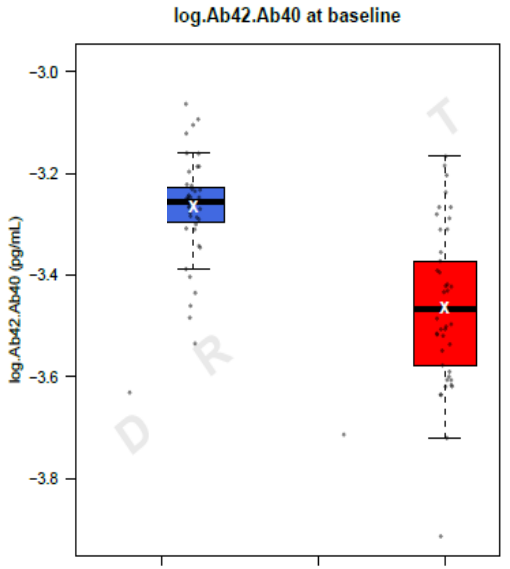

Drug exposure = C_{max} for both drugs

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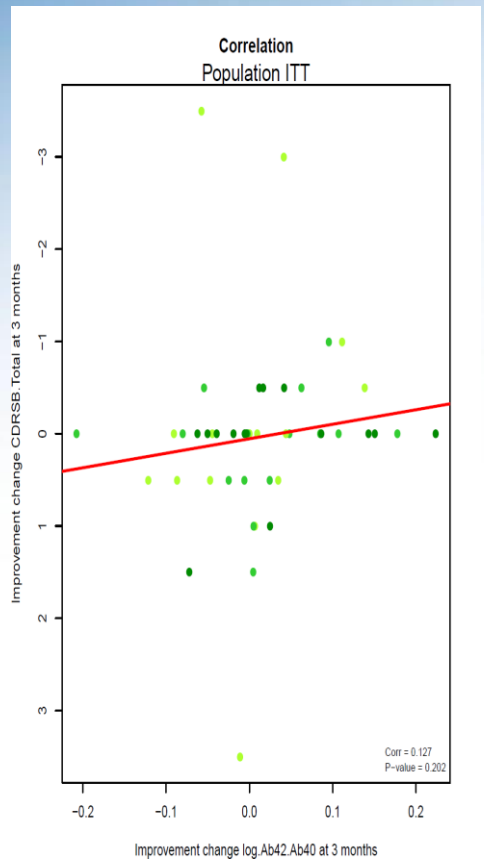
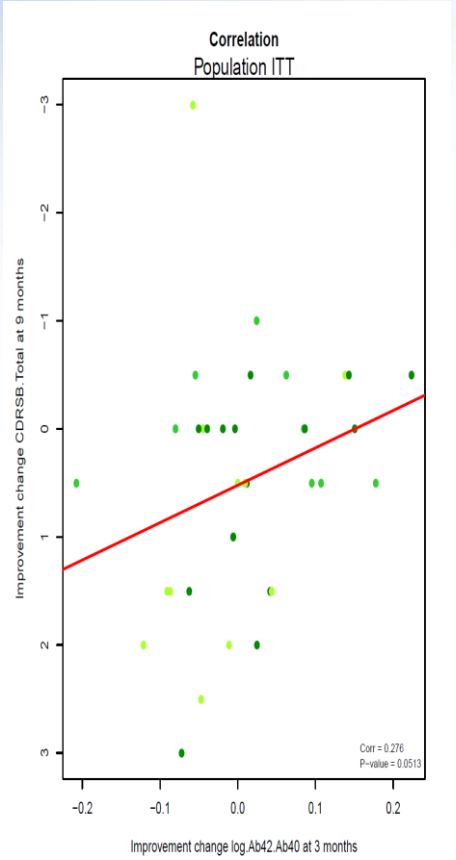
Plasma $A\beta_{42/40}$ 3-Month Improvement Corelates With Clinical Improvement: At 9 Months Rather Than At 3 Months Suggesting a "From Molecular To Clinical" Delayed Effect

3-Month CDR-SB improvement

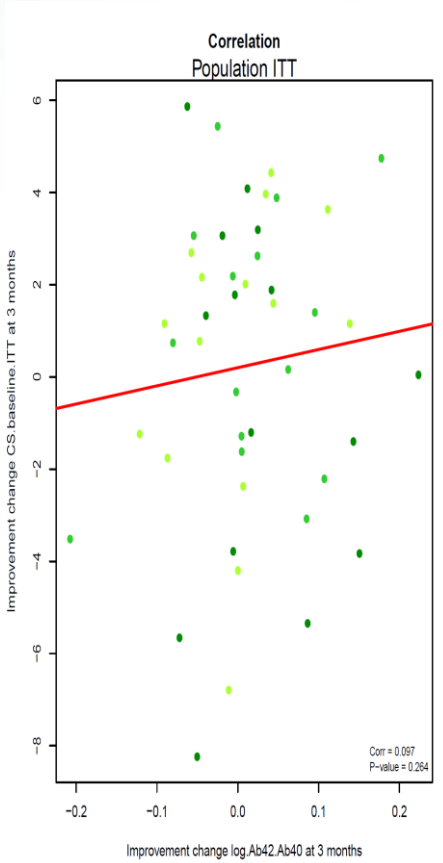


9-Month CDR-SB improvement

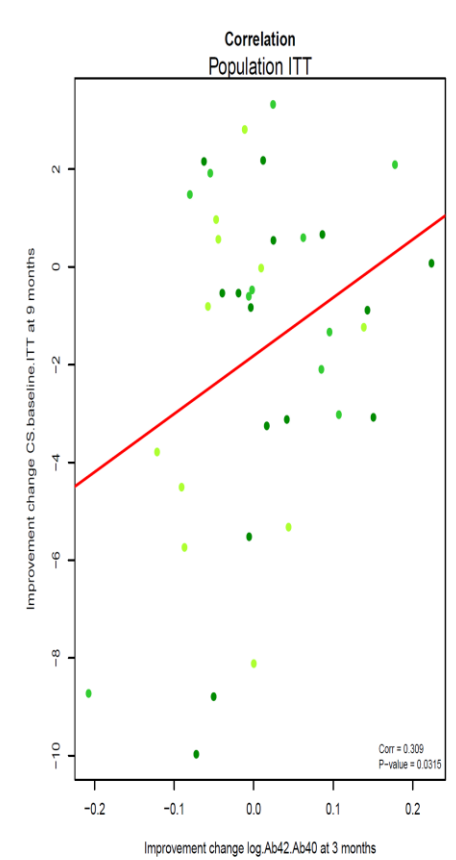


Biomarker 3-Month improvement

3-Moth Composite score (CS)* improvement



9-Moth Composite score (CS) improvement



Biomarker 3-Month improvement

* Composite score of all clinical endpoints.

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PXT864 in Alzheimer's Disease Overview

Higher doses of PXT864 have potential to demonstrate a sustained therapeutic effect on Alzheimer's Disease, due to the following advantages:

- **Strong safety profile**
- **Can be co-administered with already approved drugs in AD**
- **Can be synergistic with other NCEs to create a powerful novel new entity**

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