RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, DOSE-RANGING, MULTICENTER STUDY IN MILD TO MODERATE ALZHEIMER'S PATIENTS

Key Inclusion Criteria:

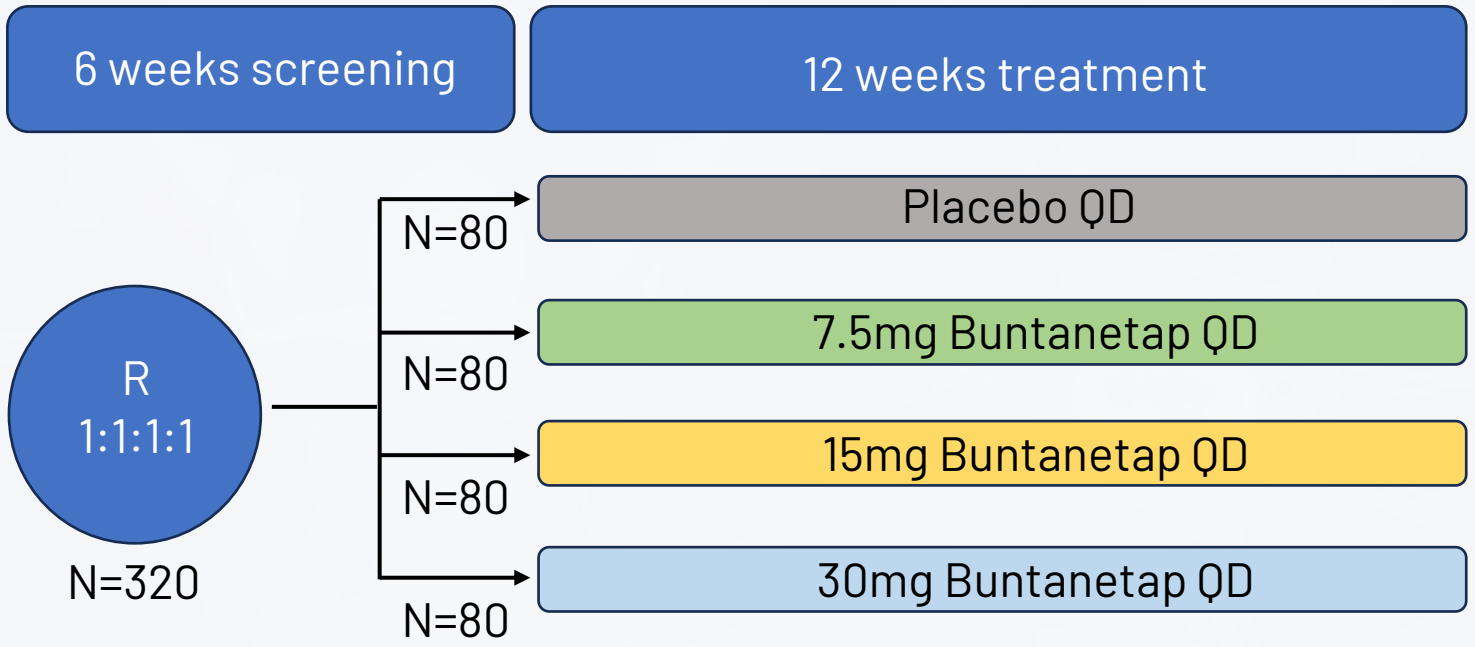
- Diagnosis of AD according to NIA and NIA-AA criteria (2011)
- Age 55 to 85
- MMSE 14-24

Key Clinical Outcome:

- Primary Endpoints:
- ADAS-Cog 11
- CGIC

Key Secondary Endpoint:

- ADCS-ADL

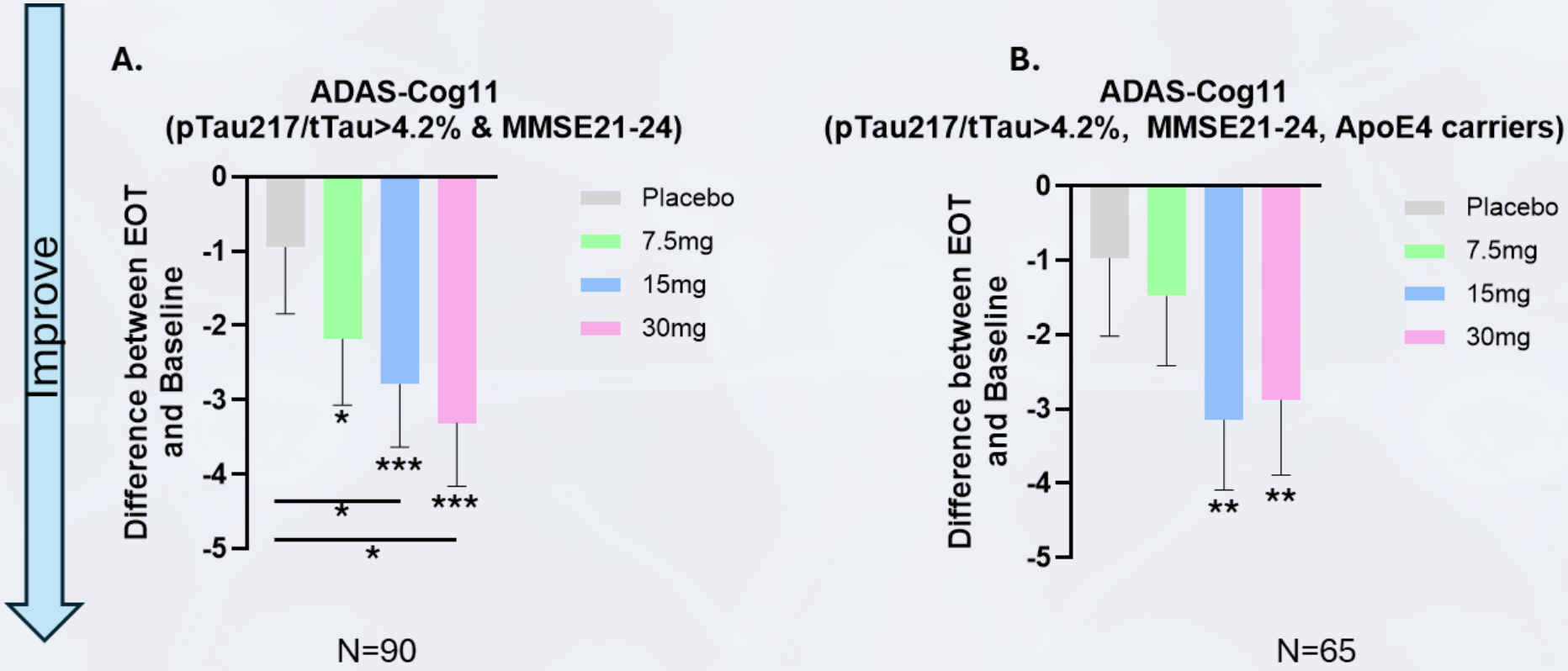


PRIMARY ENDPOINT IN ITT POPULATION (N=351)

ADAS-Cog11	Placebo (N=89)	7.5mg Buntanetap (N=88)	15mg Buntanetap (N=87)	30mg Buntanetap (N=87)
Baseline				
N	85	86	87	87
Mean Score (SD)	20.28 (6.79)	23.20 (7.59)	22.74 (7.57)	21.85 (7.16)
End of Trial (12 weeks)				
N	81	82	78	79
Mean Score (SD)	18.33 (6.94)	21.42 (8.42)	19.26 (7.70)	20.21 (8.94)
Difference from Baseline	-2.182	-1.452	-2.992	-2.304
P-value	0.001	0.001	0.001	0.001
Difference from Placebo		0.98 (0.75)	-0.68 (0.76)	0.09 (0.75)
P-value		0.193	0.366	0.910

ADAScog11 AND APOE4 STATUS

ApoE4 carrier (+/- & +/+) 66.5% in pTau217/tTau>4.2% population
vs ApoE4 carrier 22.6% in pTau217/tTau<4.2% population



Buntanetap improves ADAS-Cog11 equally in APOE4 carriers and non-carriers

SAFE IN APOE4 CARRIERS AND NON-CARRIERS IN ITT POPULATION AND EARLY AD PATIENTS

	Placebo	7.5mg Buntanetap	15mg Buntanetap	30mg Buntanetap	All Doses
APOE Carriers (N=159)	38	45	38	38	121
# TEAEs	13 (34.2%)	22 (48.9%)	17 (44.7%)	12 (31.6%)	51 (42%)
# TEAEs Related to Study Drug	1 (2.6%)	8 (17.8%)	6 (15.8%)	3 (7.9%)	17 (14%)
# Serious TEAEs	3 (7.9%)	0	0	1 (2.6%)	1 (2.5%)
# Serious TEAEs Related to Study Drug	0	0	0	0	0
APOE Non-Carriers (N=159)	41	34	43	41	118
# TEAEs	9 (22.0%)	4 (11.8%)	11 (25.6%)	17 (41.5%)	32 (27.1%)
# TEAEs Related to Study Drug	1 (2.9%)	1 (2.9%)	2 (4.7%)	3 (7.3%)	6 (5.1%)
# Serious TEAEs	0	0	0	2 (4.9%)	2 (1.7%)
# Serious TEAEs Related to Study Drug	0	0	0	0	0

AE = Adverse Event
TEAE = Treatment Related Adverse Event

RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTICENTER STUDY IN MILD TO MODERATE PARKINSON'S PATIENTS

Key Inclusion Criteria:

- Diagnosis of idiopathic PD (Postuma 2015)
- H&Y score =1, 2 or 3 during ON-state & OFF-state <2hrs per day.
- 40 – 85 years

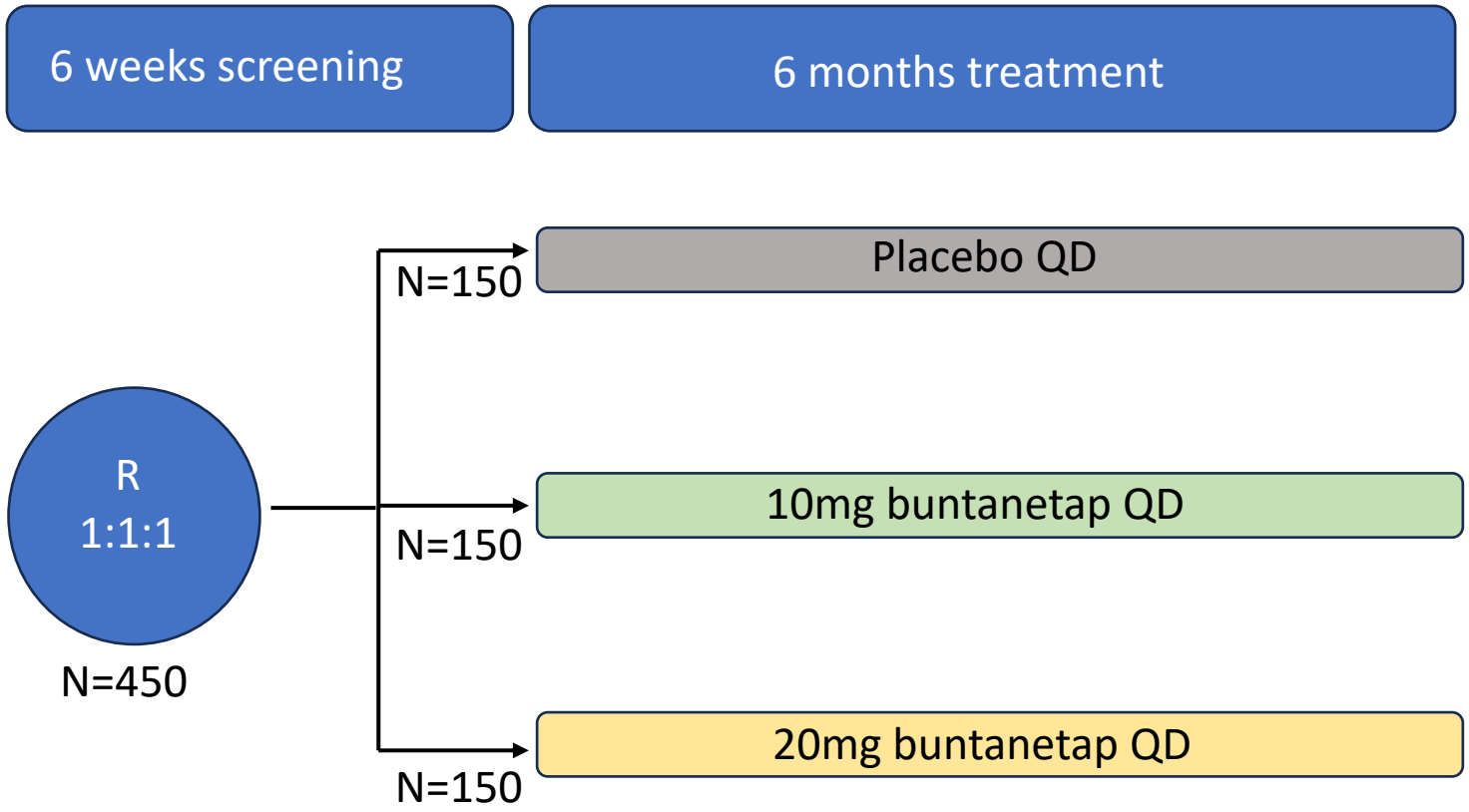
Key Clinical Outcome:

Primary Endpoint:

- MDS-UPDRS Part II (OFF state)

Key Secondary Endpoint:

- MDS-UPDRS Part II+III (OFF state)
- MDS-UPDRS Part III (OFF state)



ITT N= 523; COMPLETERS N= 471; AND SUB-POPULATIONS

Patients with >3 year PD diagnosis
(HY = 1, 2;
HW>3 years = 34%)

Selection was based on patients with deficit in MDS-UPDRS II which resulted in them showing deficits in MDS-UPDRS II, II+III, and Total.

They responded to buntanetap by improving all deficit scales

Patients with Postural Instability and Gait Difficulty
(PIGD = 21%)

These patients were diagnosed with postural instability and gait difficulty (PIGD). These patients declined faster and improved more when dosed with buntanetap.

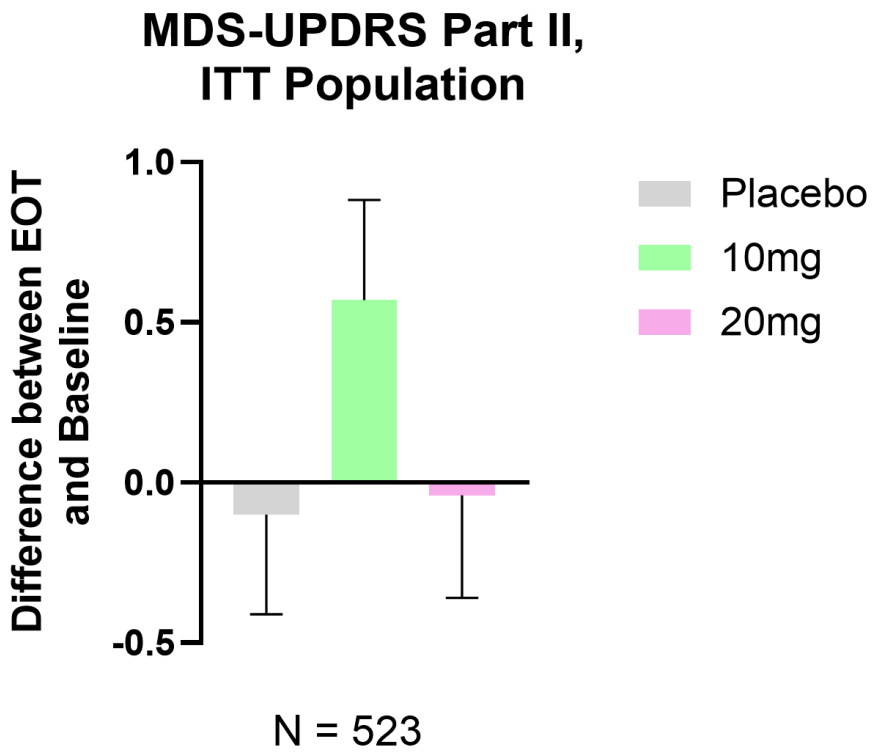
Like in the previous subpopulation, PIGD patients responded by improving all deficit scales

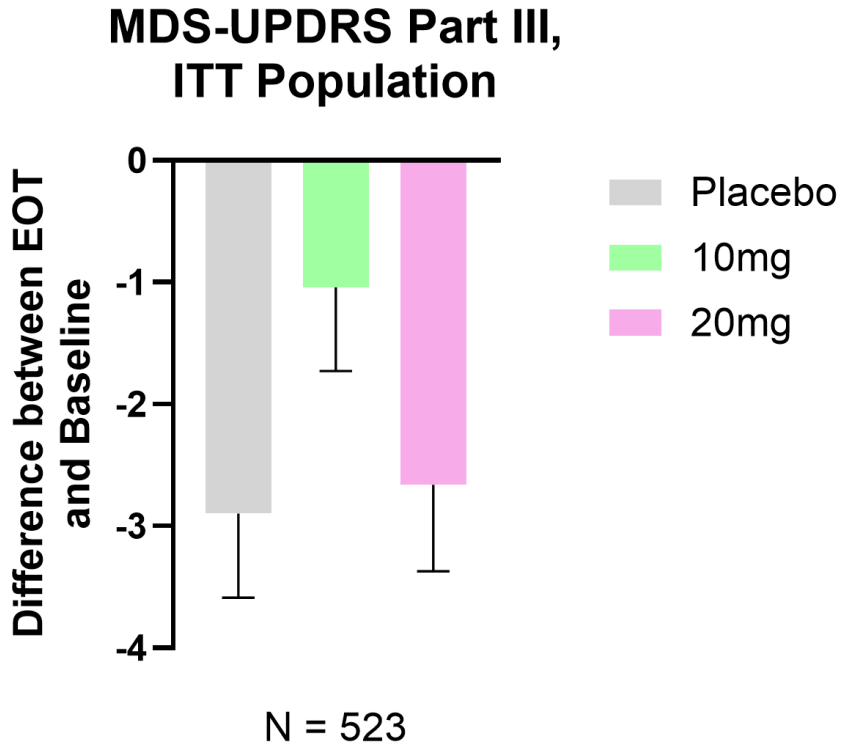
Patients with impaired cognition
(MMSE (20-30) = 100%
MMSE (20-26) = 12%)

MMSE and cognition was an exploratory endpoint. However, PD patients declined over 6 months, while treated patients remained the same.

Placebo patients with existing cognitive impairment declined while patients on buntanetap improved

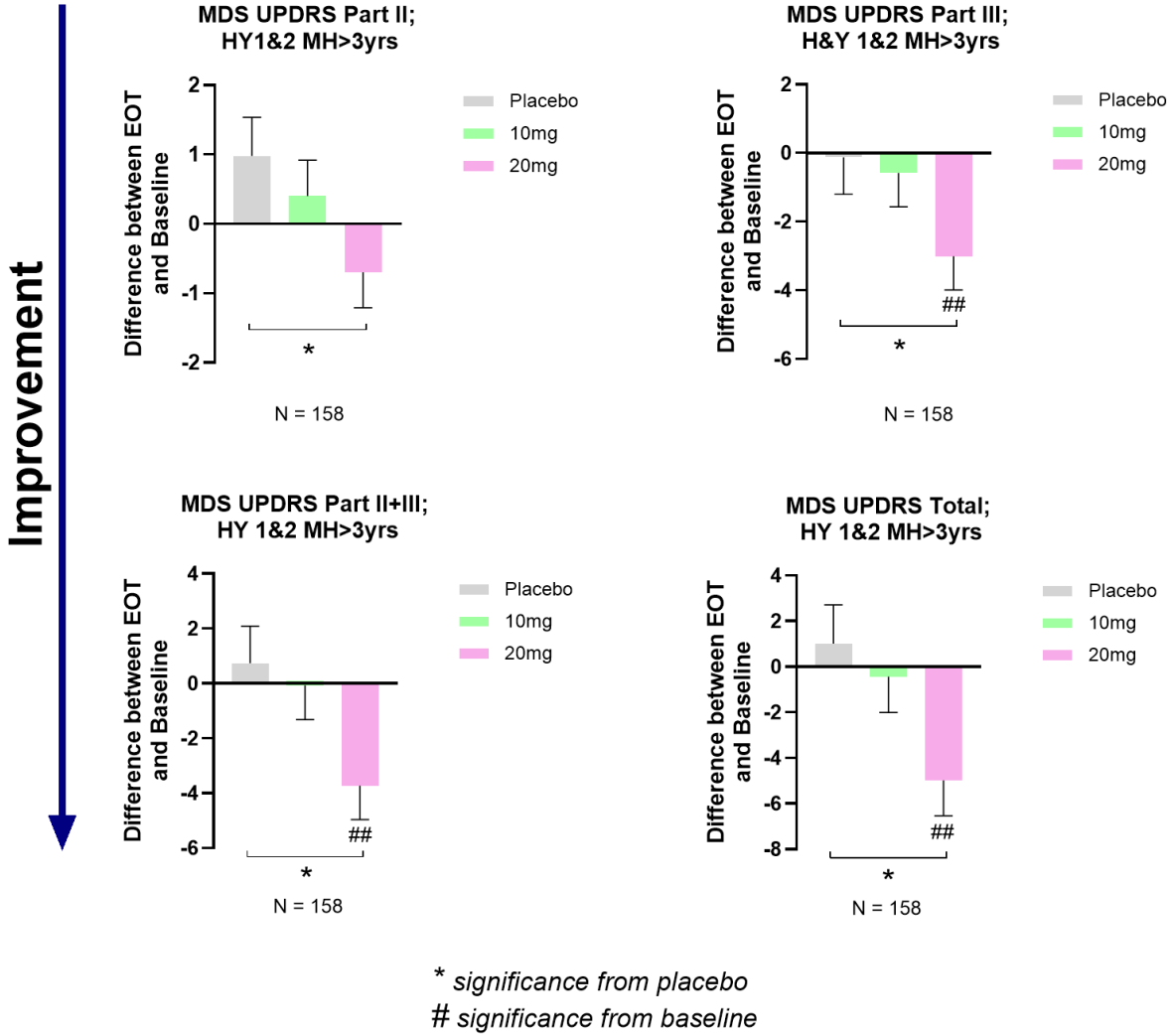
ITT Population, MDS-UPDRS II and III





Buntanetap did not show an effect in the whole ITT population, neither in MDS-UPDRS Part II or Part III.

PRIMARY AND SECONDARY ENDPOINTS IN PD PATIENTS



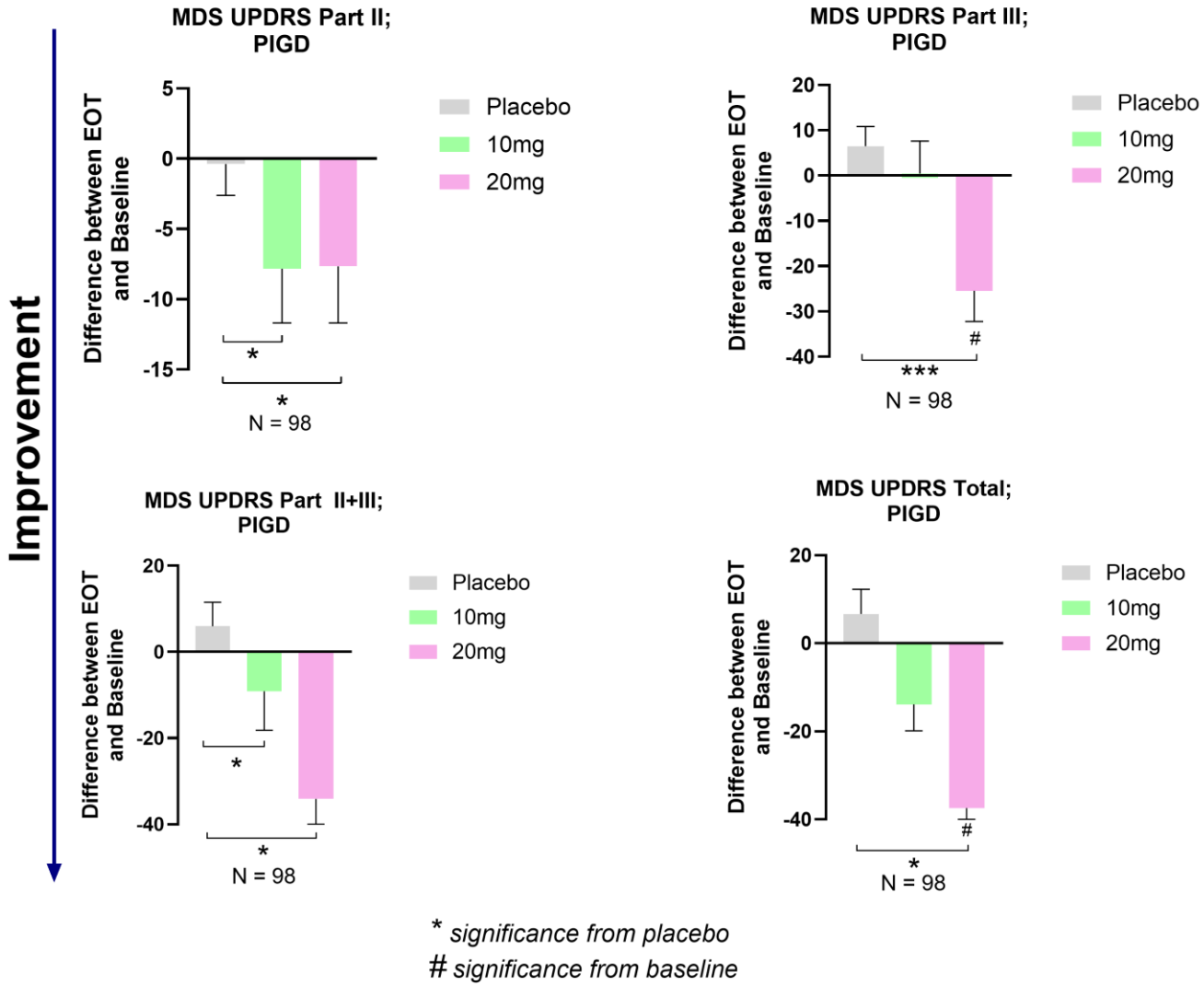
** significance from placebo*
 # significance from baseline

Buntanetap statistically and clinically significantly improved scores in all MDS-UPDRS parts in patients with a >3 years PD diagnosis.

PRIMARY AND SECONDARY ENDPOINTS IN PIGD PATIENTS

Patients diagnosed with **P**ostural **I**nstability and **G**ait **D**ifficulty-predominant disease (PIGD) are considered to having faster disease progression*.

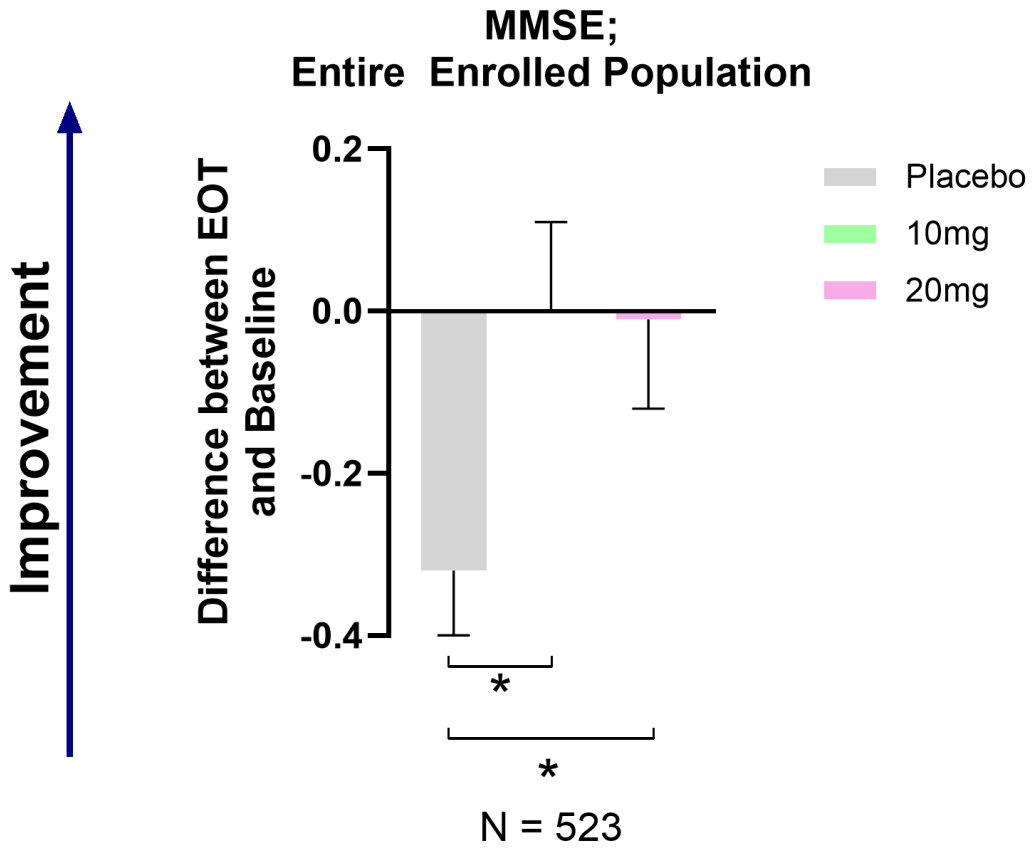
Buntanetap significantly improved MDS-UPDRS Part II, III, II+III and Total in PIGD patients.

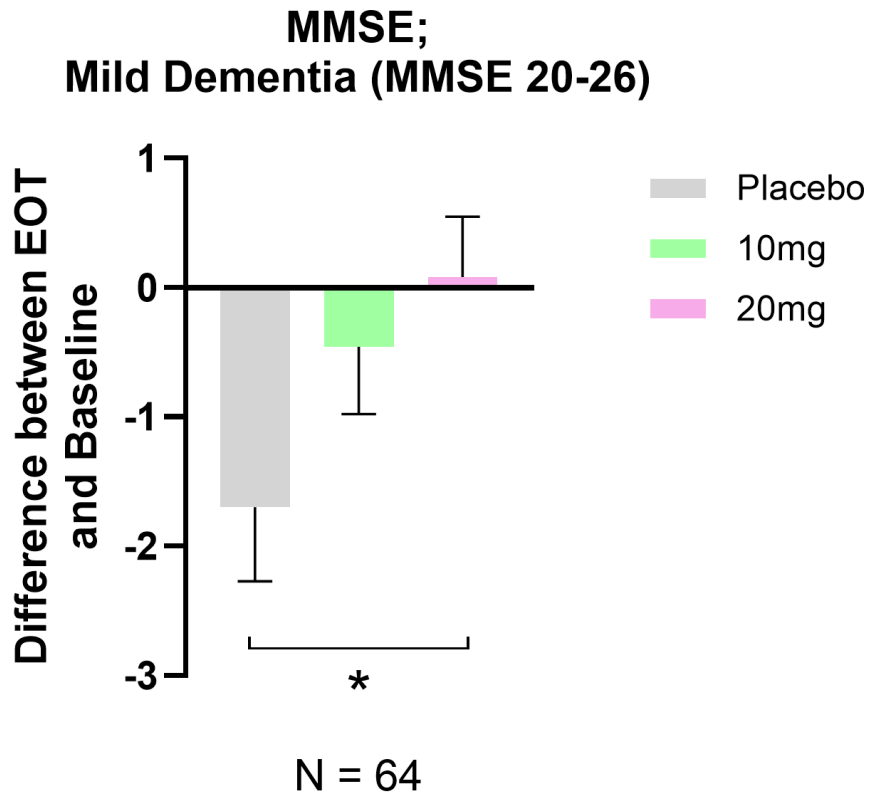


* *significance from placebo*
\# *significance from baseline*

**Jankovic et al. 1990 & Stebbins et al. 2013*

MMSE AND DEMENTIA STAGE





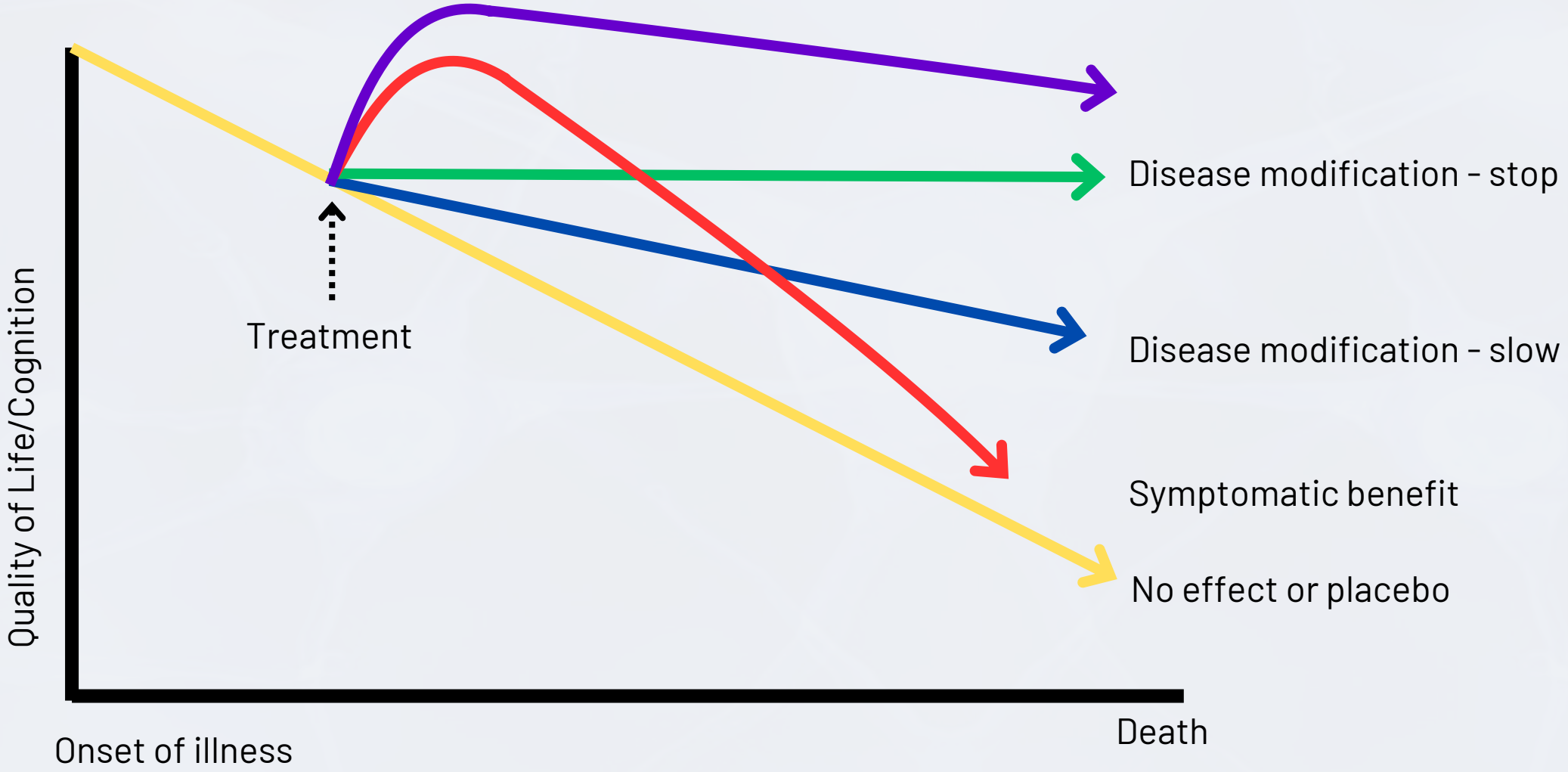
In the ITT (intent-to-treat), or the entire enrolled population, PD patients on placebo declined by 0.4 MMSE in 6 months, while all treated patients did not worsen. Only 12% showed cognitive decline as measured by MMSE 20-26. These patients declined by 1.5 MMSE points and did not decline at all when treated with buntanetap.

SAFE IN ITT PD POPULATION

	Placebo	10 mg Buntanetap	20mg Buntanetap	All Doses
	176	174	173	774
# Subjects with any AEs	91 (51.7%)	98 (56.3%)	108 (62.4%)	297 (56.8%)
# Subjects with TEAEs	86 (48.9%)	96 (55.2%)	105 (60.7%)	287 (54.9%)
# Subjects with Serious TEAEs	5 (2.8%)	4 (2.3%)	11 (6.4%)	20 (3.8%)
# Subjects with TEAEs Related to Study Drug	28 (15.9%)	28 (16.3%)	26 (15.9%)	82 (15.7%)
# Subjects with Serious TEAEs Related to Study Drug	0	0	0	0

AE = Adverse Event
TEAE = Treatment Related Adverse Event

DISEASE MODIFICATION VERSUS SYMPTOMATIC BENEFIT IN THE TREATMENT OF ALZHEIMER'S



Kennedy GJ. Primary Psychiatry. Vol 14. No 11. 2007, adapted Annovis