Safinamide, a New Anti-Parkinson Agent, is Effective and well-tolerated in Early Parkinson's Disease PD Patients on a Stable Dose of a Single DA-Agonist: Results of a Randomized, International, Placebo-controlled, Phase III Trial.

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Rationale for the use of safinamide as add-on to patients on DA-agonist

- DA-agonists are increasingly used as first-line therapy for newly diagnosed PD patients
- Although effective initially, long-term studies suggest many patients experience decrease of efficacy in motor control by third year, and need adjunctive medications, generally L-dopa
- Treatments that could reduce loss of efficacy of DA-agonists when given in combination and delay onset of use of L-dopa may provide a medical added value
- New medications acting through different mechanisms may have an advantage
- Safinamide, a new chemical entity that combines MAO-B inhibition, dopamine re-uptake, and glutamate release inhibition may respond to these challenges

Safinamide: Pharmacology

- Selective, reversible inhibitor of MAO-B
  - IC_{50}: 9.3 nM (human platelets)
  - Selectivity for MAO-B/MAO-A: 5000 times (rats); 1000 times (humans)
- Dopamine uptake blockade (IC_{50} 3.75 μg/g)
- Inhibits stimulated release of glutamate (IC_{50} 2.82 μg/g)
- Blockade of N-type Ca^{++} channels and use/frequency-dependent Na^{+} channels
- In vivo pharmacology:
  - Prevention/reversal of MPTP-induced deficits
  - Efficacy in "wearing-off" model (6-OHDA rats)
  - Neuroprotective in MCA occlusion, kainic acid models

Study 015/017 design

- Double-blind, placebo-controlled, parallel-group, randomised, multi-national (I, SP, UK, IND,ARG,CHI, COL) Phase III trial.
- Dose comparative study (safinamide 50-100 and safinamide150-200 mg/day, versus placebo) in 270 patients with early PD.
  - DA-agonist plus placebo (n=90)
  - DA-agonist plus safinamide 50-100 mg/day (n=90)
  - DA-agonist plus safinamide 150-200 mg/day (n=90)
- Eligible patients treated for a total of 1.5 years. This period of 1.5 years, for analysis purposes is achieved by the patients participating in two sequential studies:
  - Study 015 (24 weeks)
  - Study 017, its extension phase (52 weeks).
- Data from the first 6 months of treatment (#015) were analyzed, and the investigators, CRAs and medical monitors remained blinded to the treatment assignment for the additional year of treatment (#017).

Study 015 - Efficacy variables

Primary endpoint:

- Change in mean value of UPDRS-III total score from baseline to endpoint (mixed linear model)

Secondary endpoints:

- CGI - Change from baseline to endpoint (proportion of patients showing improvement – scores of 1, 2 or 3)
- Responder rate (at least 30% improvement of the UPDRS-III between baseline and endpoint)
- Change from baseline to endpoint for the UPDRS–II (ADL) total score
- Change from baseline to endpoint in cognition, as measured by the Cogtest battery
- Change from baseline to endpoint in EuroQOL

Study 015: Inclusion Criteria

- Male or non-fecund female, aged 30-80 years.
- Patients meeting London Brain Bank criteria for idiopathic Parkinson's disease of less than 5 years duration
- Diagnosis based on medical history and neurological examination
- Hoehn and Yahr stages I-III
- Stable dose of a single dopamine agonist for at least 4 weeks

Study 015: Main Exclusion Criteria

- End of dose wearing off, “on-off” phenomenon, disabling peak dose or biphasic dyskinesias or unpredictable fluctuations
- Use of any anti-Parkinsonian medication, other than a single DA-agonist in 4 weeks preceding screening
- Current use of more than one dopamine agonist
- Dementia or cognitive dysfunction: MMSE <24 or score of 3 on item I of UPDRS section I
- Presence of mental or physical condition (e.g. neurosis, arthritis) that would preclude collection of safety/efficacy data
- Patients with severe, unstable, or serious medical conditions

Dose Titration: Overview

Study Day	Dose Level	Low Dose Safinamide (50-100mg/day)	High Dose Safinamide(150-200mg/day)	Placebo
1	1	50 mg	100 mg	Placebo
7	2	50 mg	150 mg	Placebo
14	3	100 mg	200 mg	Placebo

Demographic and disease characteristics (ITT population)

Parameter	LOW dose (N=90)	HIGH dose (N=89)	Placebo (N=90)
Age in years (mean ± SD)	56.5±11.3	58.5 ± 11.7	57.3±10.8
Male [N (%)]	59 (65.6%)	54 (60.7%)	56 (62.2%)
Weight in kg (mean ± SD)	72.3 ± 13.8	68.0 ± 12.5*	69.3 ± 13.9
RACE [N (%)]			
• American Indian or Alaska Native	4 (4.4%)	1 (1.1%)	1 (1.1%)
• Black or African American	0 (0.0%)	1 (1.1%)	0 (0.0%)
• White	51 (56.7%)	52 (58.4%)	55 (61.1%)
• Asian (Indian)	35 (38.9%)	35 (39.3%)	34 (37.8%)
SMOKING HISTORY [N (%)]			
• Current use YES	10 (11.1%)	5 (5.6%)	11 (12.2%)
ALCOHOL USE [N (%)]			
• Current use YES	15 (16.7%)	15 (16.9%)	22 (24.4%)
DURATION OF DISEASE			
• Time since diagnosis (years)	2.64±1.42	2.3±1.32	2.41±1.2
HOEHN & YAHR			
• Baseline mean (range)	1.84 (1-3)	1.86 (1-3)	1.90 (1-3)
CGI-SEVERITY			
• Baseline mean ± SD	3.1 ± 0.79	3.1 ± 0.85	3.1 ± 0.76
UPDRS-III			
• Baseline mean ± SD	22.0±10.1	19.3±9.8	20.7±9.6

N = number of patients; % = percentage of patients
***p<0.05 vs. Low Dose**

Overall subject disposition

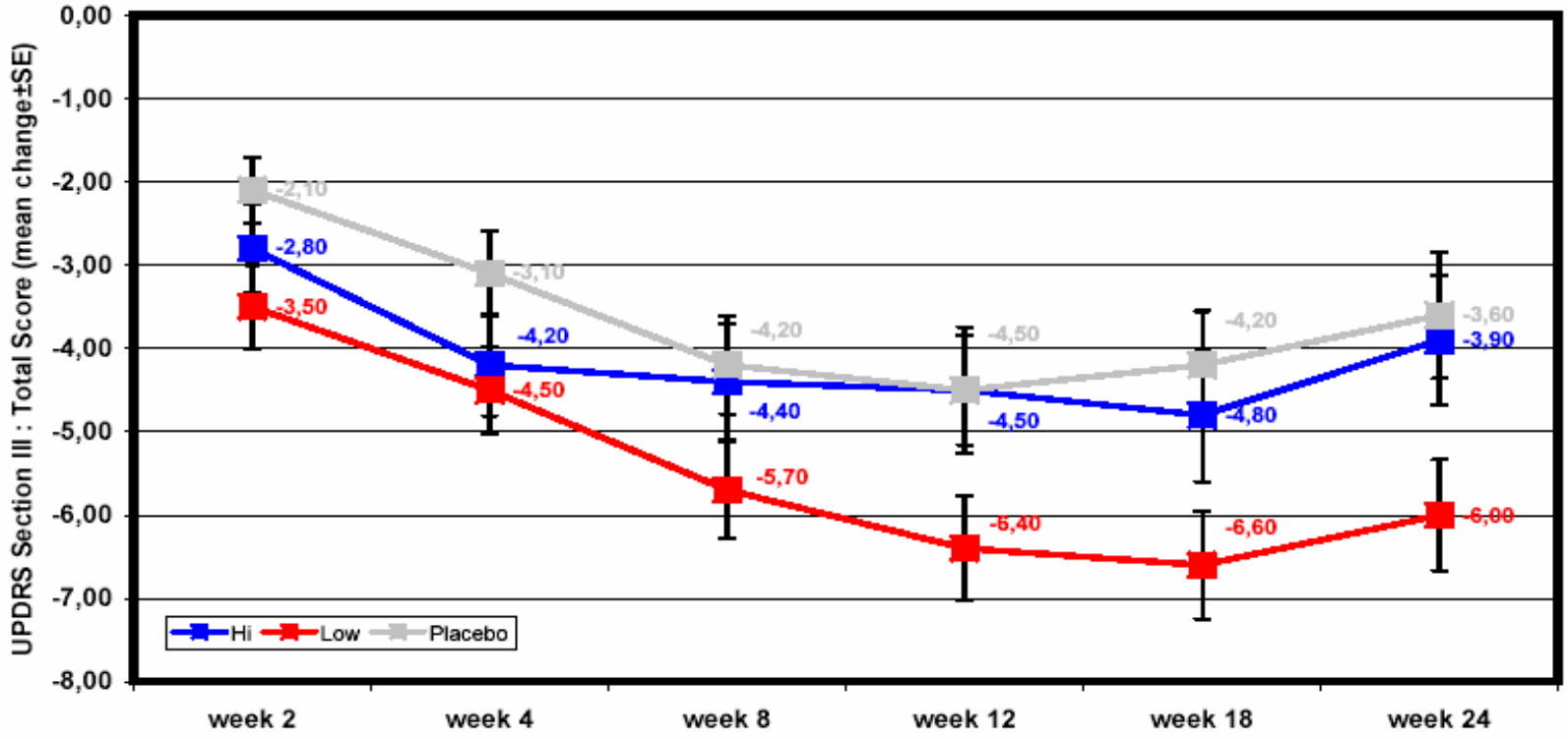
	LOW dose (N=90)	HIGH dose (N=89)	Placebo (N=90)
Screened	**293**		
Randomized	**90 (100 %)**	**89 (100 %)***	**90 (100 %)**
Subjects completing 24 weeks	**81 (90.0 %)**	**70 (78.7 %)**	**81 (90 %)**
Premature Discontinuation*			
• Death	0	1 (1.1 %)	0
• Serious Adverse Events	2 (2.2 %)	2 (2.2 %)	0
• Adverse Drop-outs	2 (2.2 %)	4 (4.5 %)	2 (2.2 %)
• Withdrawal of consent	3 (3.3 %)	7 (7.9 %)	7 (7.8 %)
• Lack of efficacy	0	2 (2.2 %)	0
• Other	3 (3.3 %)	5 (5.5 %)	0
Total Premature Discontinuation	**9 (10.0 %)**	**19 (21.3 %)**	**9 (10.0 %)**

* Patients may be present in more than one cathegory

Mean change from baseline in UPDRS III Mixed linear model (ITT population)

	Low dose		High dose		Placebo	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Baseline value	90	22.0 ± 10.1	89	19.3 ± 9.8	90	20.7 ± 9.6
Week 2	87	-3,5 ± 4,9	86	-2,8 ± 4,7	88	-2,1 ± 3, 7
Week 4	86	-4,5 ± 5,6	80	-4,2 ± 4,7	86	-3,1 ± 4,7
Week 8	85	-5,7 ± 6,4	78	-4,4 ± 5,1	85	-4,2 ± 5,4
Week 12	85	-6,4 ± 7,0	79	-4,5 ± 5,6	87	-4,5 ± 6,1
Week 18	82	-6,6 ± 7,2	74	-4,8 ± 5,55	84	-4,2 ± 5,9
Endpoint change	86	-6,0 ± 7,2	81	-3,9 ± 6,0	87	-3,6 ± 7,1
Endpoint value	86	16.3 ± 9.0	81	15.6 ± 9.6	87	17.1 ± 8.8
p-value	**0.0419**		**0.6504**			
95% CI	**[-3.7; -0.1]**		**[-2.3; 1.4]**			
Point estimate	**-1.9**		**-0.4**			

UPDRS Section III : Total Score
Population : ITT (No Imputation of Missing Data) ref.: Table 14.2.1

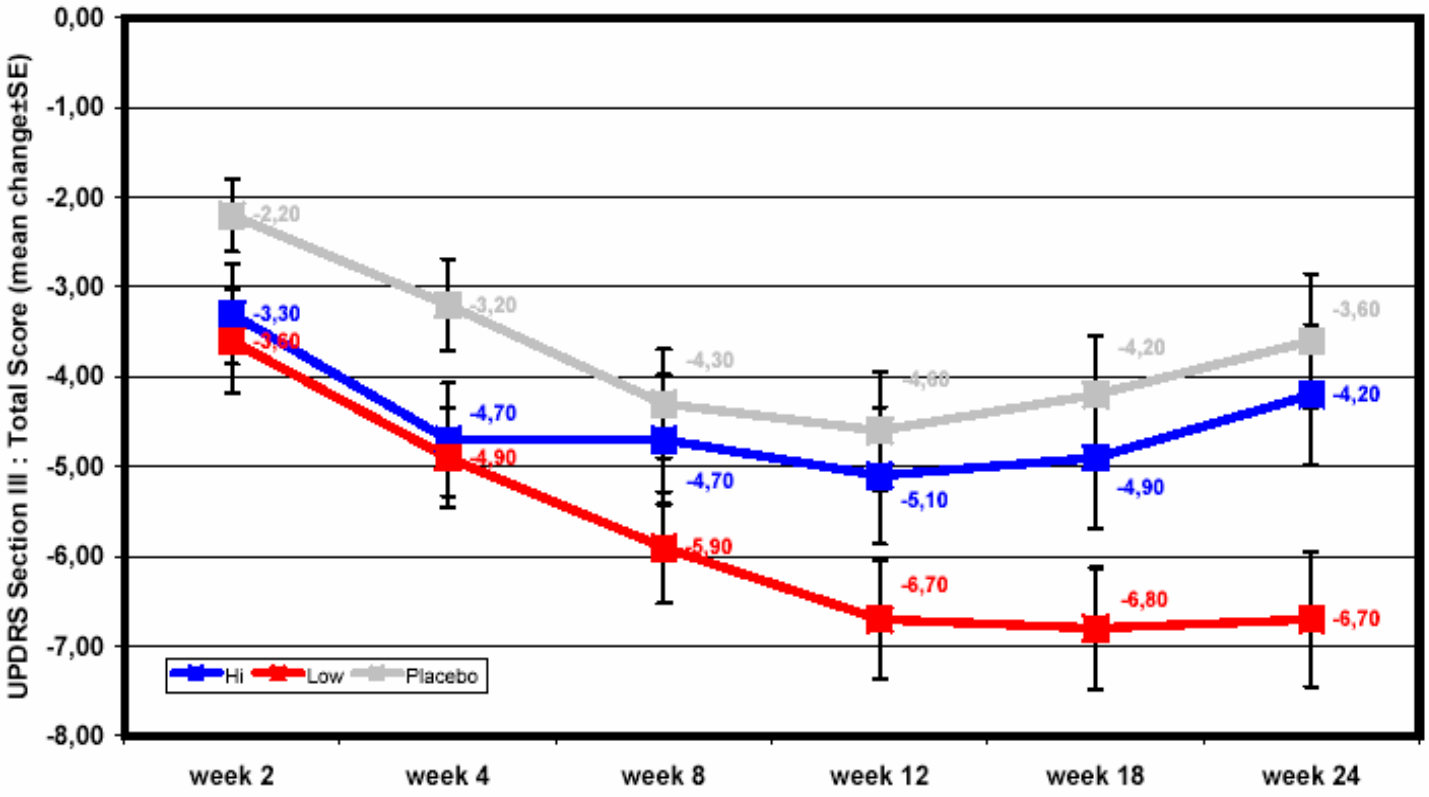


	week 2	week 4	week 8	week 12	week 18	week 24
High N=	86	80	78	79	74	81
Low N=	87	86	85	85	82	86
Placebo N=	88	86	85	87	84	87

A mixed linear model is used to calculate a point estimate, 95% CI and p-value for the difference between active treatment groups and Placebo in the change from Baseline to Endpoint. The unstructured covariance structure was used as output.

	Hi	Low
95% CI	[-2.3,1.4]	[-3.7,-0.1]
Point Estimate	-0,4	-1,9
p-value	0,6504	0,0419

UPDRS Section III : Total Score
Population : ITT with Various Imputation Schemes ref.: Table 14.2.2
OC=OBSERVED CASE



	week 2	week 4	week 8	week 12	week 18	week 24
High N=	70	70	70	70	70	70
Low N=	81	80	81	81	81	80
Placebo N=	82	82	82	82	82	82

Change from Baseline to Endpoint is analysed using ANCOVA with treatment and country as main effects and Baseline score as covariate. Point estaimates and 95% CI for the difference between active treatment groups and Placebo are calculated from this ANCOVA.

	Hi	Low
95% CI	[-2.8, 1.0]	[-4.3, -0.6]
Point Estimate	-0,9	-2,4
p-value	0,3327	0,0111

Mean change from baseline in UPDRS III ITT with Various Imputation Schemes - OC and RDO

		Low dose		High dose		Placebo	
		Value	Change	Value	Change	Value	Change
Baseline	N	84		73		86	
	Mean	22,70		19,60		20,80	
	SD	10,05		10,38		9,79	
Endpoint	N	81	81	72	72	86	86
	Mean	16,20	-6,60	15,60	-4,10	17,20	-3,60
	SD	9,03	7,02	9,73	6,27	8,90	7,11
95% CI		[-4.2, -0.5]		[-2.8, 0.9]			
Point Estimation		-2.3		-0.9			
p value		0.0125		0.3245			

Change from baseline to endpoint analysed using ANCOVA with treatment and country as the main effect, and baseline score as the covariate. Point analysis and 95% CI for the difference between active treatment groups, and placebo are calculated from this ANCOVA

Mean change from baseline in UPDRS II –– LOCF analysis

	Low dose		High dose		Placebo	
	N	Mean ± SD	N	Mean ± SD	N	Mean ± SD
Baseline value	90	8.2 ± 4.9	89	7.3 ± 4.7	89	8.1 ± 5.3
Week 2	87	-1.7 ± 2.9	86	-1.0 ± 2.2	88	-0.8 ± 2.6
Week 4	86	-2.3 ± 2.7	80	-1.3 ± 2.4	86	-1.4 ± 2.6
Week 8	85	-2.5 ± 3.2	78	-1.9 ± 2.4	85	-1.8 ± 2.8
Week 12	85	-2.6 ± 3.3	79	-1.9 ± 2.9	87	-1.5 ± 3.1
Week 18	82	-2.6 ± 3.6	74	-2.0 ± 2.7	84	-1.2 ± 3.2
Endpoint change	90	-2.2 ± 3.8	89	-1.4 ± 2.7	89	-1.2 ± 3.5
Endpoint value	90	6.0 ± 4.3	89	5.9 ± 4.5	89	6.8 ± 4.4
p-value	**0.0248**		**0.2762**			
95% CI	**[-1.8, -0.1]**		**[-1.3, 0.4]**			
Point estimate	**-1.0**		**-0.5**			

Mean change from baseline in EUROQoL –– LOCF analysis

		Low dose		High dose		Placebo	
		Value	Change	Value	Change	Value	Change
Baseline	N	90		89		90	
	Mean	2.2		2.2		2.5	
	SD	1.8		1.8		1.7	
Endpoint (LOCF)	N	88	88	85	85	88	88
	Mean	1.9	-0.3	1.8	-0.4	2.4	-0.1
	SD	1.7	1.6	1.6	1.4	1.6	1.8
95% CI		[-0.8, 0.03]		[-0.82, 0.02]			
Point Estimate		-0.381		-0.401			
p value		0.072		0.06			

Most frequent Adverse Events

Treatment group	Safinamide 50-100 mg N=90	Safinamide 150-200 mg N=89	Placebo N=90
	%	%	%
Patients with AEs	63.3	52.8	52.2
Nausea	7.8	9.0	6.7
Headache	4.4	4.5	8.9
Abdominal pain upper	6.7	1.1	4.4
Cough	6.7	5.6	4.4
Pyrexia	5.6	5.6	6.7
Vomiting	5.6	2.2	6.7
Back pain	5.6	3.4	3.3
Dizziness	5.6	4.5	2.2
Gastritis	4.4	5.6	2.2
Hypertension	0	5.6	3.3

Key Results for safinamide add-on in PD patients on a single DA-agonist

- Statistically significant benefits seen with safinamide 50-100 mg/day on:
  - motor symptoms (UPDRS III): mean change, responder rate (≥ 30% improvement)
  - Activities of Daily Living (UPDRS II)
  - Benefit in Quality of Life (EUROQoL)
  - Clinical Global Impression of severity (CGI-S)/change (CGI-C)
- Preliminary analysis of cognitive function has shown exciting results:
  - Baseline cognitive deficits improved with safinamide treatment
  - Cognitive domains improved: executive function, spatial and working memory
- No increase in side effects, labs, ECG, or blood pressure (normal diet)
- Phase III effective dose-range of 50-100 mg/day (mean 90 mg/day), confirms effective dose (~ 80 mg/day) in phase II studies;

Key Results for safinamide add-on in PD patients on a single DA-agonist

- No incremental benefit of 150-200 mg/day compared to DA-agonist monotherapy for UPDRS-III mean change and UPDRS-II
  - Statistically significant improvement compared to DA-agonist monotherapy for UPDRS-III Responder Rate (30% improvement from baseline)
  - Significant benefit compared to DA-agonist monotherapy for CGI-C Responder Rate (improvement Vs no change/worsening)
- No benefit over 50-100 mg/day of safinamide in any analysis
- Future trials to evaluate doses of 50-100 mg/day of safinamide
- Phase III study of safinamide as add-on to L-dopa in “fluctuators” currently ongoing

Study 015/017 - Participating sites

Argentina

Giannaula R., Buenos Aires, ***Merello M.***, Buenos Aires

Chile

Miranda M., Santiago, ***Saez D.***, Santiago

Colombia

Lorenzana P., Bogotà, ***Centanaro G.***, Bogotà, ***Takeuchi J.***, Cali-Valle

India

Borgohain R., Hyderabad, ***Bhatt M.***, Mumbai, ***Behari M.***, New Delhi, ***Shah A.***, Mumbai, ***Roy A.K.***, Bangalore

Italy

Stocchi F., Rome, ***Onofrj M***., Chieti-Pescara, ***Abruzzese G.***, Genova, ***Barone P.***, Napoli, ***Battistin L.***, Padova, ***Lamberti P.***, Bari, ***Marconi R***., Grosseto, ***Monge A***., Rome, ***Nordera G.P***.,Vicenza

Spain

Kulisevsky J., Barcelona, ***Lozano J.***, Madrid, ***Vazquez A.***, Madrid

United Kingdom

Shapira A.H., London, ***Barker R.A.***, Cambridge