

Supplement to: Overall Efficacy and Safety of Safinamide in Parkinson's Disease: A Systematic Review and a Meta-Analysis

Journal: Clinical Drug Investigation

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Supplementary material S1: Search Strategy

PubMed

(((((("Parkinson Disease"[Mesh]) OR (((("Idiopathic Parkinson's Disease"[Title/Abstract] OR "Lewy Body Parkinson Disease"[Title/Abstract] OR "Lewy Body Parkinson's Disease"[Title/Abstract] OR "Primary Parkinsonism"[Title/Abstract] OR "Parkinson's Disease"[Title/Abstract] OR "Parkinson's Disease, Idiopathic"[Title/Abstract] OR "Parkinson's Disease, Lewy Body"[Title/Abstract] OR "Idiopathic Parkinson Disease"[Title/Abstract] OR "Paralysis Agitans" [Title/Abstract] OR Parkinson[Title/Abstract])) OR "Parkinson Disease"[Title/Abstract]))) AND
(((("safinamide" [Supplementary Concept]) OR (Xadago[Title/Abstract] OR safinamide[Title/Abstract]))) OR ((("NW-1015" OR "FCE 28073" OR "FCE-28073" OR "PNU 151774E" OR "PNU-151774E" OR "safinamide methanesulfonate" OR "fbap methanesulfonate" OR "FCE 26743" OR "FCE-26743")))) AND (((((((("Randomized Controlled Trial "[Publication Type]) OR "controlled clinical trial"[Publication Type]) OR (randomized[Title/Abstract] OR randomised[Title/Abstract])) OR placebo[Title/Abstract]) OR randomly[Title/Abstract]) OR groups[Title/Abstract]) OR trial[Title/Abstract]) OR "drug therapy "[Subheading])) NOT "Animals"[Mesh]) NOT (("Animals"[Mesh]) AND "Humans"[Mesh]))

Embase

#1 'safinamide'/exp
#2 'safinamide' OR xadago OR 'nw-1015' OR 'fce 28073' OR 'fce-28073' OR 'pnu 151774e' OR 'pnu-151774e' OR 'safinamide methanesulfonate' OR 'fbap methanesulfonate' OR 'fce 26743' OR 'fce-26743':de,ti,ab
#3 #1 OR #2
#4 'parkinson disease'/exp
#5 'idiopathic parkinson* disease' OR 'lewy body parkinson disease' OR 'lewy body parkinson* disease' OR 'primary parkinsonism' OR 'parkinson* disease' OR 'parkinson* disease, idiopathic' OR 'parkinson* disease, lewy body' OR 'idiopathic parkinson disease' OR 'paralysis agitans' OR parkinson:de,ti,ab
#6 #4 OR #5
#7 #3 AND #6
#8 'crossover procedure':de OR 'double-blind procedure':de OR 'randomized controlled trial':de OR 'single-blind procedure':de OR random*:de,ab,ti OR factorial*:de,ab,ti OR crossover*:de,ab,ti OR ((cross NEXT/1 over*):de,ab,ti) OR placebo*:de,ab,ti OR ((doubl* NEAR/1 blind*):de,ab,ti) OR ((singl* NEAR/1 blind*):de,ab,ti) OR assign*:de,ab,ti OR allocat*:de,ab,ti OR volunteer*:de,ab,ti
#9 #7 AND #8

CENTRAL (the Cochrane Library) and CINAHL (EBSCO host)

We used below free-text terms combined with MeSH:

Safinamide AND Parkinson disease

Supplementary material S2: PRISMA checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	6
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	7-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	N/A
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8; 21
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8-9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	9-10; S5
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-11; 20-23; S6-S14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-11; 22-30
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-11; S12-S13
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	12-15; 26-30
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	15
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	8

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

Supplementary Figure S1 Risk of bias assessment

	Randomization process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall
009	+	+	?	+	-	-
015	+	+	-	+	+	-
016	+	+	?	+	+	?
MOTION	+	+	?	+	+	?
SETTLE	+	+	?	+	+	?
ME2125-3	+	+	+	+	+	+

+

Low Risk

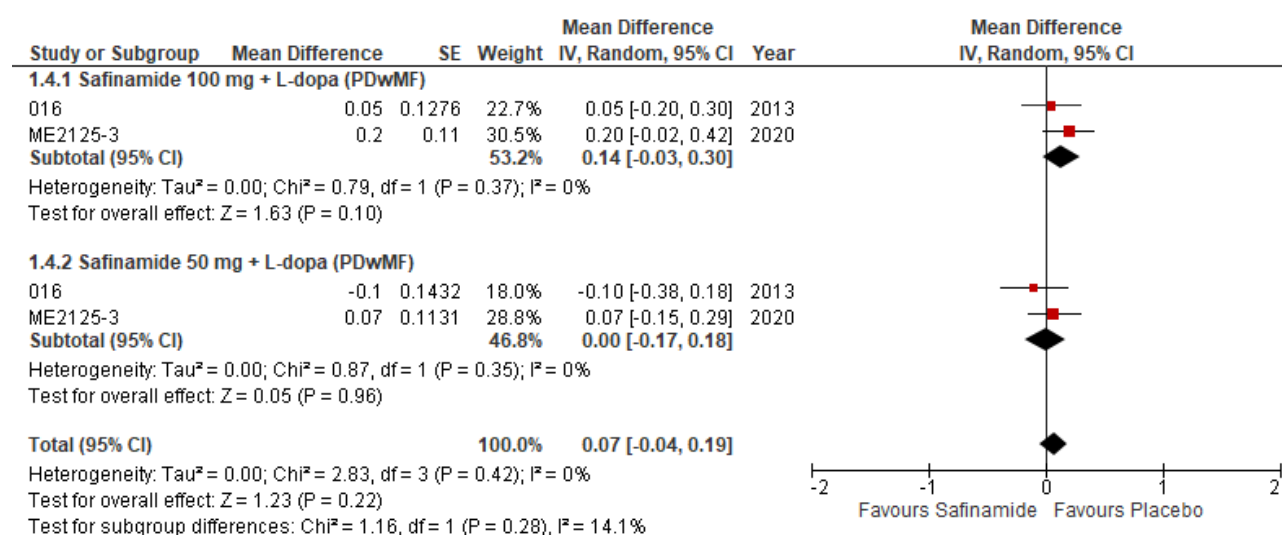
?

Some Concerns

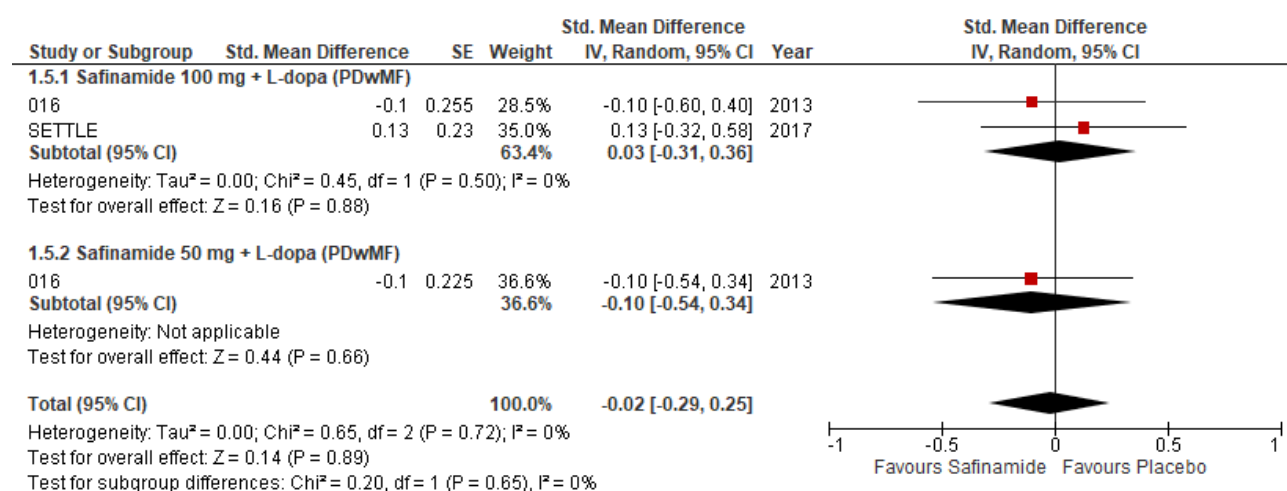
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High Risk

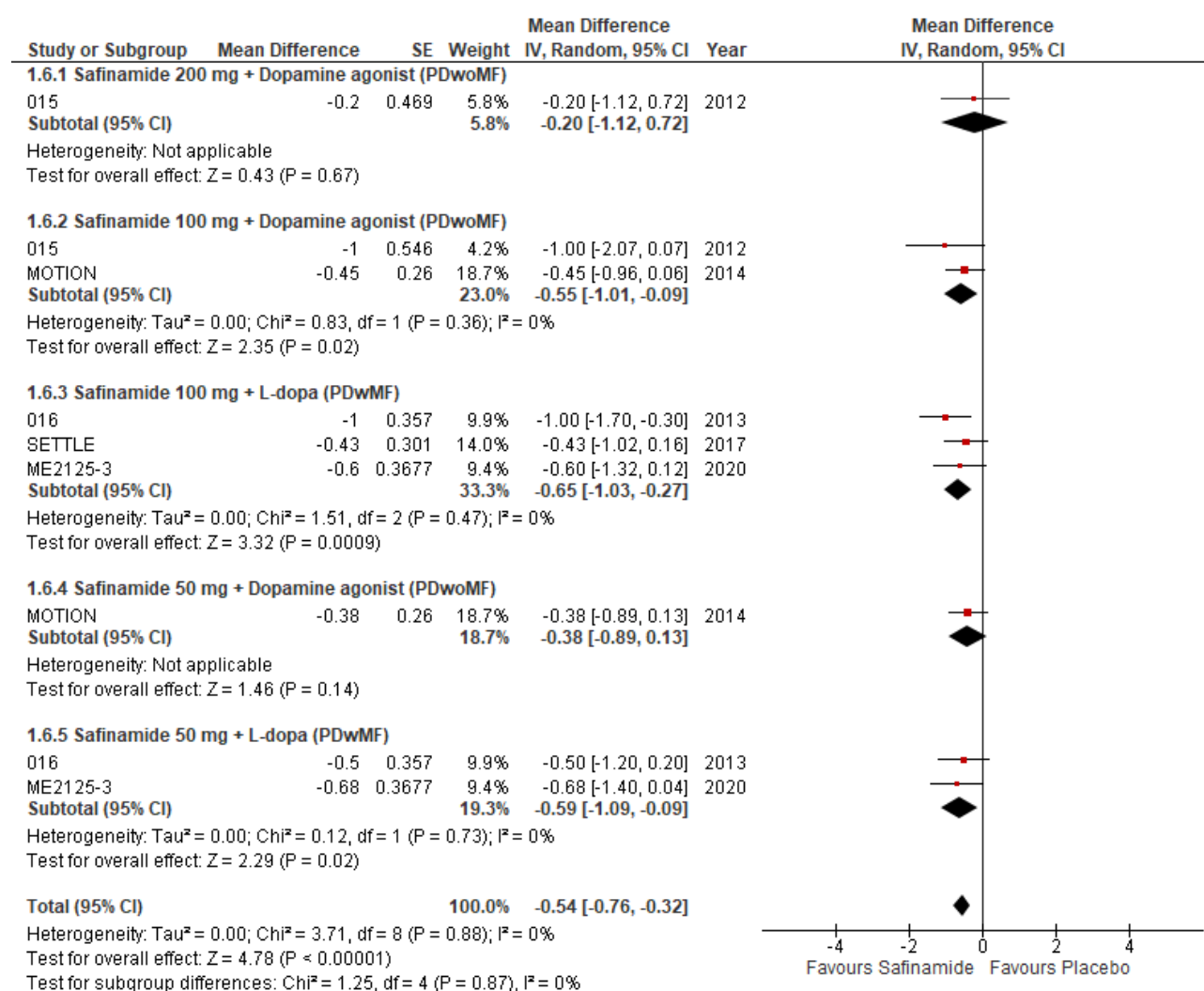
Supplementary Figure S2 ON-time with troublesome dyskinesia



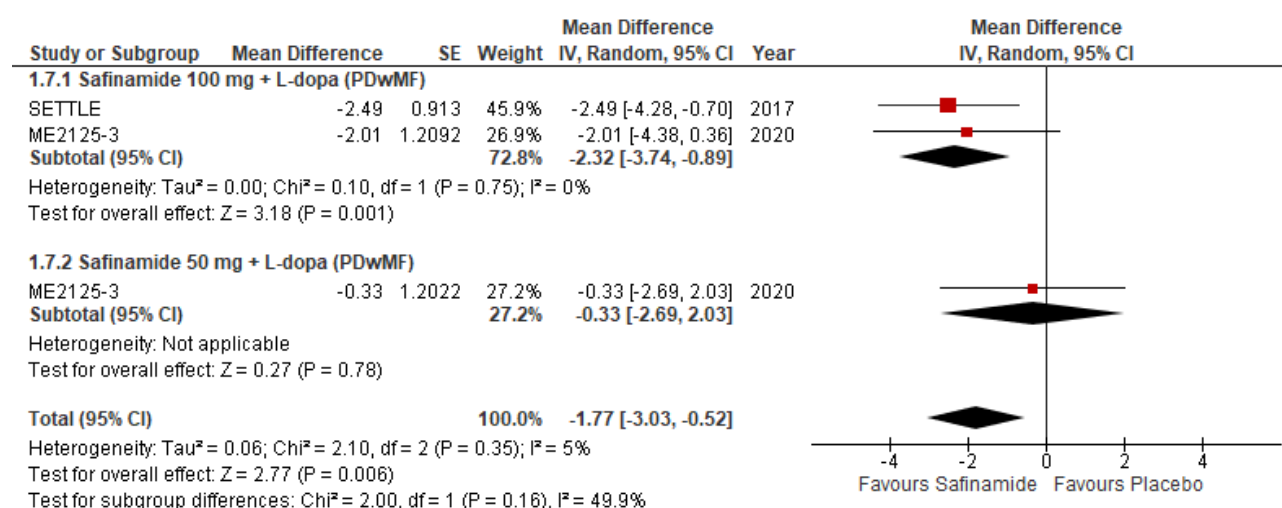
Supplementary Figure S3 Dyskinesia rating scale



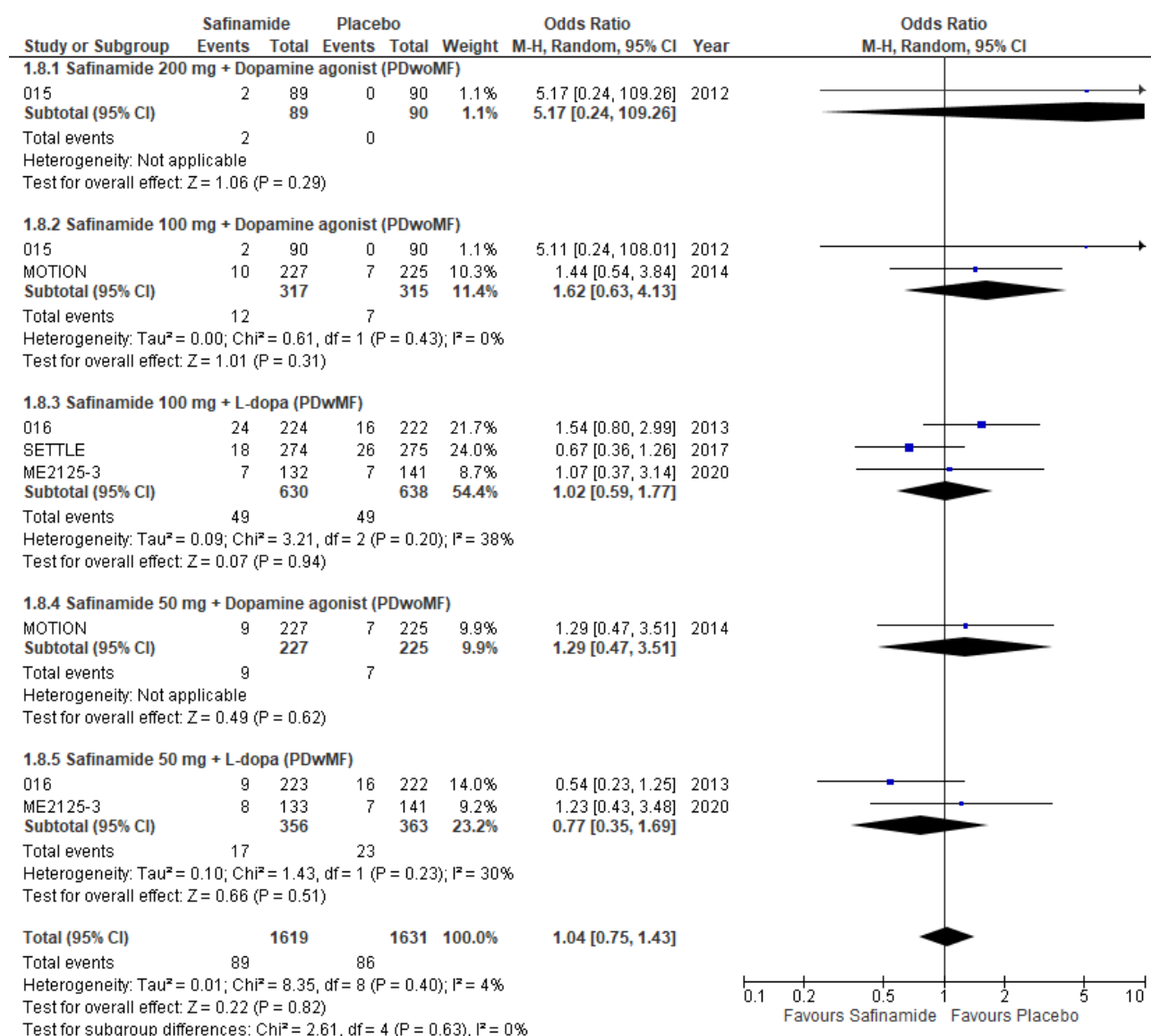
Supplementary Figure S4 UPDRS-II



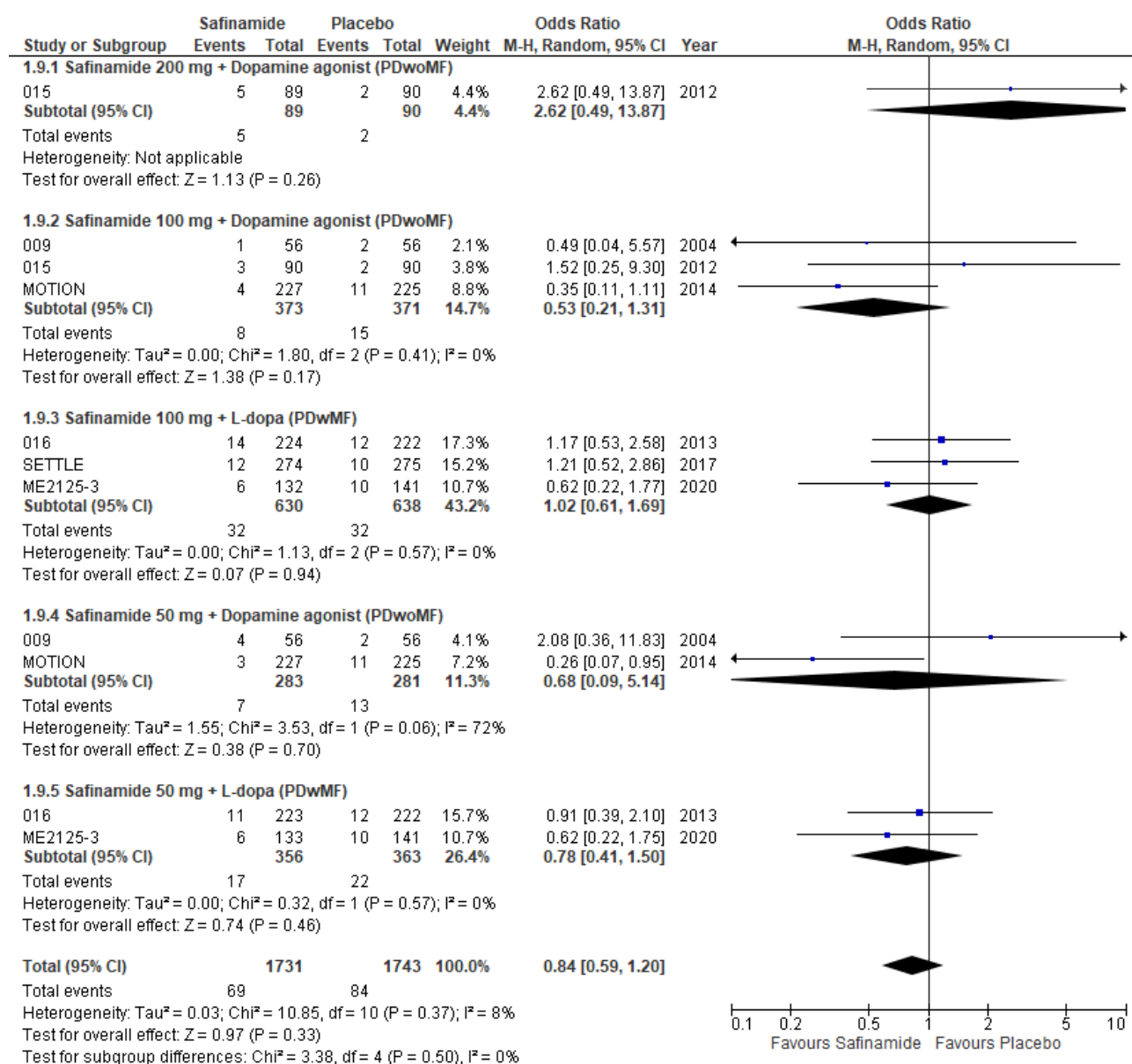
Supplementary Figure S5 PDQ-39



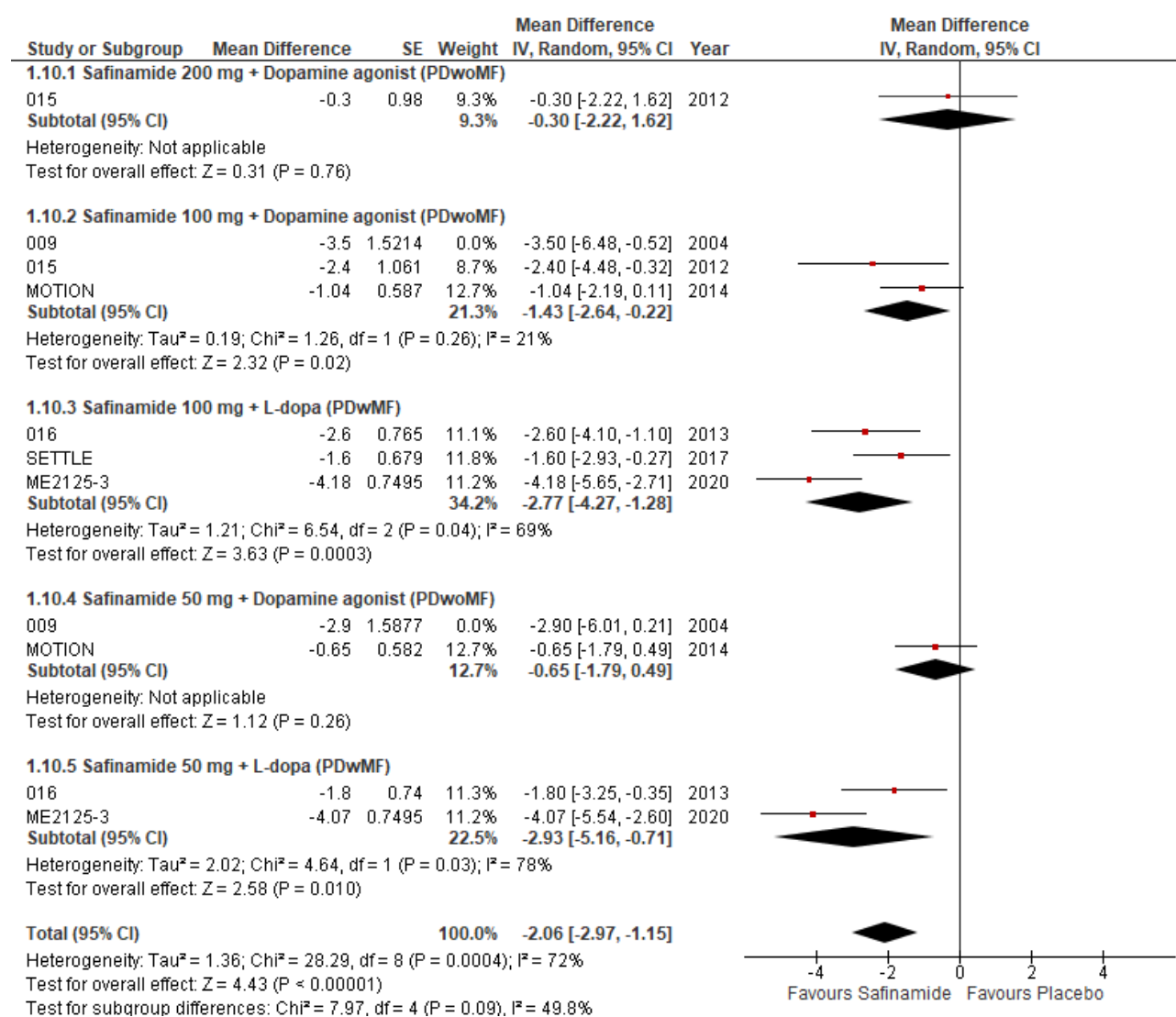
Supplementary Figure S6 SAE



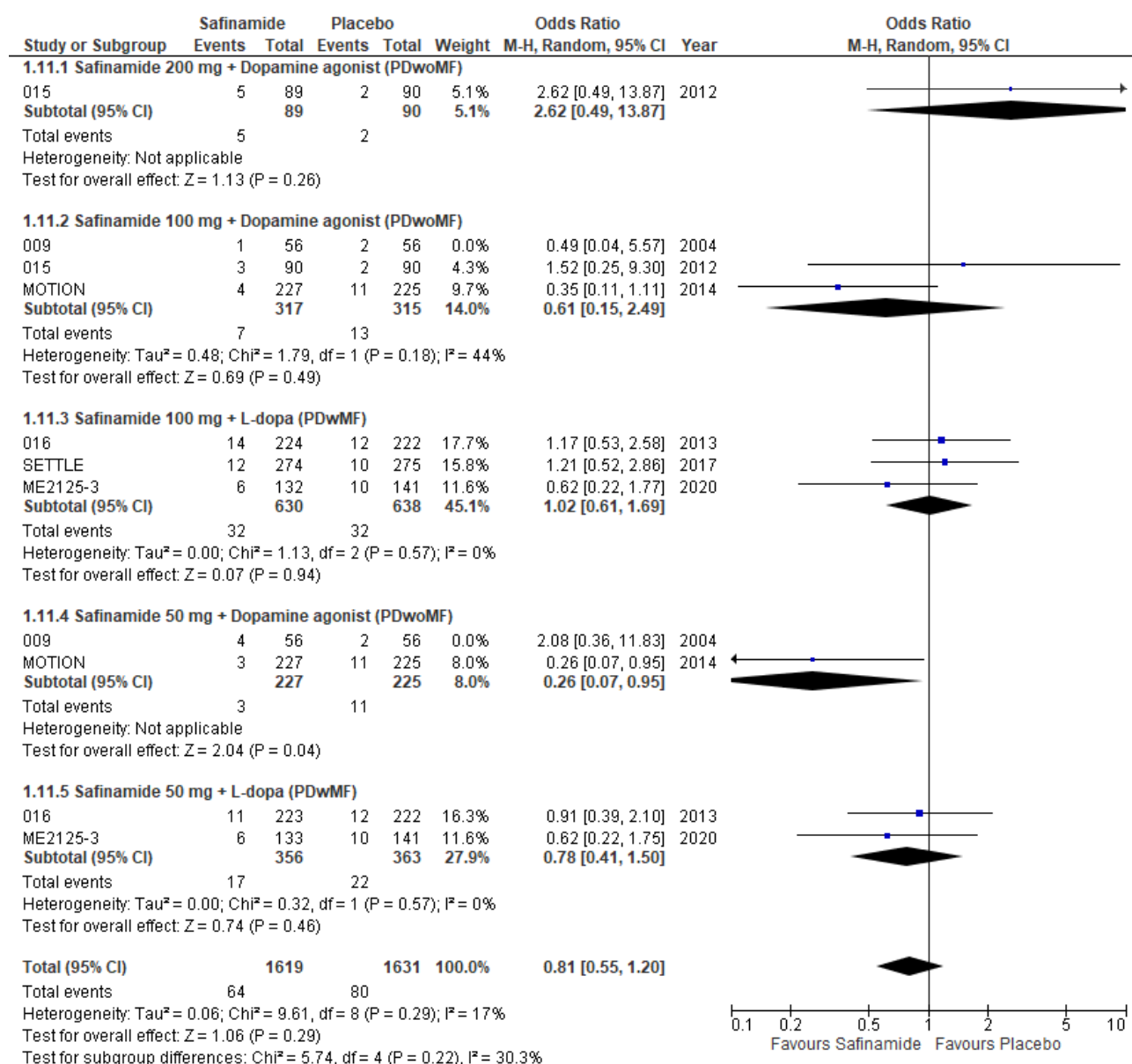
Supplementary Figure S7 Treatment discontinuation due to AEs



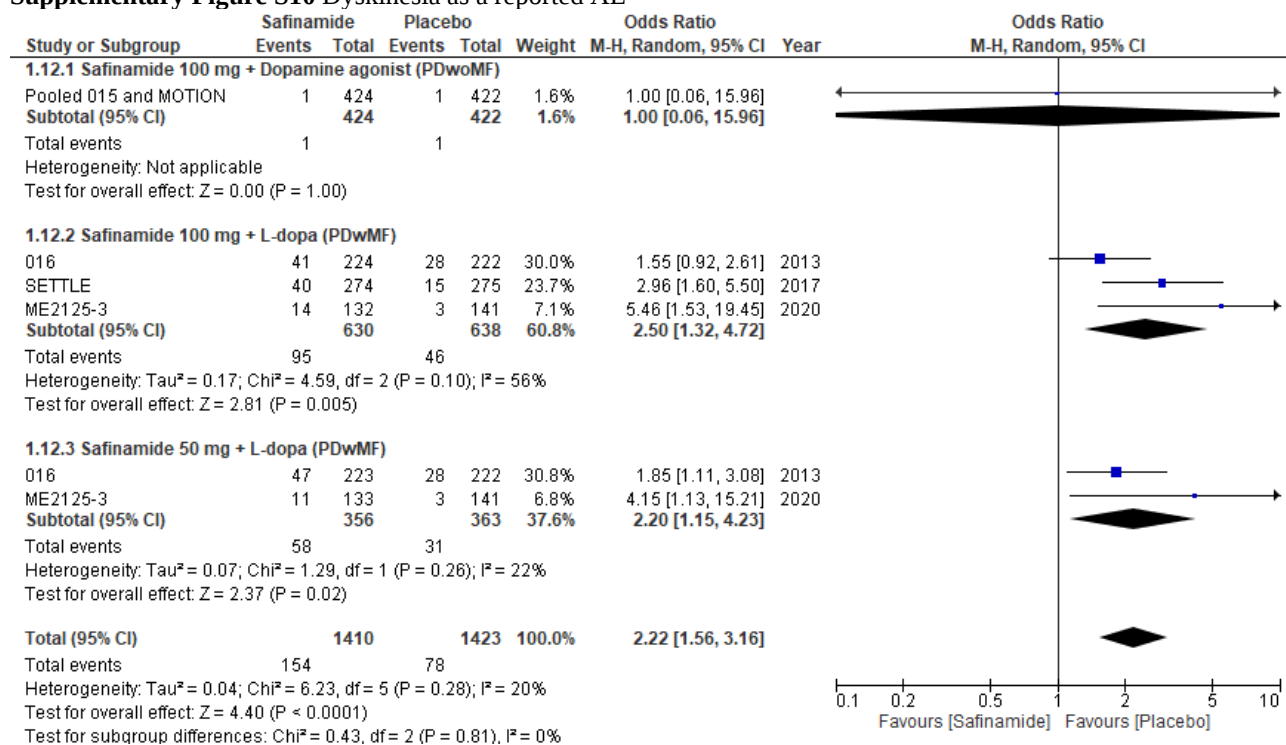
Supplementary Figure S8 UPDRS-III sensitivity analysis excluding 009 trial



Supplementary Figure S9 Treatment discontinuation due to AEs sensitivity analysis excluding 009 trial



Supplementary Figure S10 Dyskinesia as a reported AE



Supplementary Table S1 AEs causing discontinuation (from 015, MOTION, 016, and SETTLE pooled treatment arms)

	PDwMF; safinamide + dopamine agonist					PDwMF; safinamide + Ldopa					
	50 mg N (%)	100 mg N (%)	200 mg N (%)	PBO N (%)	Total N (%)	50 mg N (%)	100 mg N (%)	PBO N (%)	Total N (%)	50 mg vs PBO OR (95% CI)	100 mg vs PBO OR (95% CI)
Safety population, N	226	317	89	315	947	223	498	497	1218	721	994
AE											
Paresthesia	0 (0.0)	1 (0.3)	1 (1.1)	0 (0.0)	2 (0.2)	1 (0.4)	1 (0.2)	0 (0.0)	2 (0.2)	NA	NA
Tremor	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	1 (0.4)	0 (0.0)	1 (0.2)	2 (0.2)	NA	NA
Dizziness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	3 (0.6)	0 (0.0)	3 (0.2)	NA	NA
Dystonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Head titubation	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Headache	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Dyskinesia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	6 (2.7)	14 (2.8)	7 (1.4)	27 (2.2)	1.94 (0.64; 5.83)	2.02 (0.81; 5.06)
Parkinson's disease	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (1.3)	7 (1.4)	2 (0.4)	12 (1.0)	NA	NA
Balance disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)	NA	NA
Presyncope	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA
Cognitive disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA
Memory impairment	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Akathisia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Skin pain	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Rash	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Blister	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA
Hyperhidrosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA
Lichen planus	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Psoriasis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Anemia (iron def)	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Nausea	1 (0.4)	0 (0.0)	2 (2.2)	2 (0.6)	4 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Abdominal pain	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	1 (0.4)	1 (0.2)	0 (0.0)	2 (0.2)	NA	NA
Diarrhea	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Gerd	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Necrotizing colitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA

Vomiting	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.1)	1 (0.4)	1 (0.2)	0 (0.0)	2 (0.2)	NA	NA
Aphthous stomatitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)	NA	NA
Constipation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)	NA	NA
Hematemesis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Depressed mood	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Compulsive sexual behavior	0 (0.0)	0 (0.0)	1 (1.1)	1 (0.3)	2 (0.2)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Hallucination	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	4 (0.8)	3 (0.6)	7 (0.6)	NA	NA
Impulse control disorder	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Insomnia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Libido decreased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Nervousness	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Nightmare	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Suicide attempt	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Sleep terror	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA
Bradypnea	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Psychotic disorder	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Bronchospasm	0 (0.0)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Cough	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Dysphonia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Dyspnea	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	3 (1.3)	0 (0.0)	1 (0.2)	4 (0.3)	NA	NA
Pneumonitis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)	NA	NA
Dyspnea exertional	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Fatigue	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Asthenia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	1 (0.2)	0 (0.0)	2 (0.2)	NA	NA
Chest discomfort	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)	NA	NA
Oedema peripheral	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Hyponatremia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Hypertension	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	NA	NA
Orthostatic hypotension	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Basal cell carcinoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	3 (0.6)	1 (0.2)	4 (0.3)	NA	NA
Breast cancer	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA

Non-Hodgkin lymphoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA
Acute lymphocytic leukemia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Muscle spasms	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	0 (0.0)	2 (0.2)	NA	NA
Muscle rigidity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	1 (0.2)	2 (0.2)	NA	NA
Back pain	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.2)	NA	NA
Musculoskeletal stiffness	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Pain in extremity	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.1)	NA	NA
Arrhythmia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA
Palpitations	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)	NA	NA
Ventricular tachycardia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA
Cataract subcapsular	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA
Blurred vision	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.2)	NA	NA
Dry eye	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.2)	NA	NA
Electrocardiogram change	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA
Prolonged QT	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	1 (0.2)	2 (0.2)	NA	NA
Urinary tract infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.1)	NA	NA
Fall	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA
Subdural hematoma	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA
Cachexia	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.2)	0 (0.0)	1 (0.1)	NA	NA

AEs causing treatment discontinuation extracted from 015, MOTION, 016, and SETTLE studies. ORs were calculated for any AEs causing discontinuation in a proportion superior than 2.0% of included patients. Doses from different studies are pooled together.

PDwoMF=Parkinson's disease without motor fluctuations; PDwMF= Parkinson's disease with motor fluctuations; PBO=placebo; CI=confidence interval; AE=adverse event; OR=odds ratio; NA=not applicable.