OBSERVATIONAL STUDY

European multicenter retrospective-prospective cohort study to observe Safinamide safety profile and pattern of use in clinical practice during the first post-commercialization phase– Study Z7219N02

FINAL STUDY REPORT

Version 1.6, 05/06/2020

Signature page

This study protocol has been carefully reviewed and agreed upon by:

Global Head Medical Affairs CNS

CARLO CATTANEO

22/6/2020 Carlo Cattaneo

Date, signature

For Contract Research Organization

Study Coordinator

Firmato da:
ORI ALESSANDRA
Motivo:
Approval Signature
Alessandra ORI

Data: 22/06/2020 15:06:31

Date, signature

Statistician

Lucia SIMONI

Lucia 22/06/2020

Date, signature

PASS information

Title	European multicenter retrospective-prospective cohort study to observe Safinamide safety profile and pattern of use in clinical practice during the first post-commercialization phase– Study Z7219N02
Version identifier of the final study report	*1.6*
Date of last version of the final study report	*05/06/2020*
EU PAS register number	EUPAS13745
Active substance	Safinamide (N04BD03)
Medicinal product	Xadago® 50 mg and 100 mg film-coated tablets
Product reference	Marketing Authorisation numbers: EU/1/14/984/001-10
Procedure number	EMEA/H/C/002396
Marketing authorisation holder(s)	Zambon S.p.A.
Joint PASS	No

Research question and objectives	During the initial marketing authorization procedure, at day 180, the European Medicines Agency (EMA) recommended that the Applicant provide additional real world data on safinamide given the uncertainties regarding categories of patients not well represented in clinical trials, namely patients aged > 75 and those with concomitant psychiatric conditions. Following this request, a Drug Utilization Study (DUS) aimed at investigating how safinamide is prescribed and used in routine clinical practice was designed, including also Parkinson's Disease (PD) patients with relevant concomitant diseases. Primary objective: To describe the occurrence of adverse events in patients treated with safinamide in real-life conditions during one year in its first post-commercialization phase as reported by the Investigators. The analysis was conducted overall and in some subgroups of interest, namely in patients aged >75 and those with relevant concomitant conditions. Secondary objectives: 1. To describe the characteristics of patients treated with safinamide according to clinical practice (demographics, disease duration, disease severity, previous treatment for PD, concomitant relevant conditions with particular focus on psychiatric ones and related treatments). 2. To describe safinamide treatment patterns in real-life setting (treatment duration, dose adjustments and interruptions, dose discontinuation and reason, changes in concomitant PD therapies, treatments for PD administered after safinamide).
Country(-ies) of study	Belgium, Germany, Italy, Spain, Switzerland, United Kingdom. The study protocol reported also France among countries, but finally the drug was not reimbursed and no patients were recruited

Author	Zambon S.p.A., Via Lillo del Duca, 10, 20091 - Bresso (MI), Italy, Phone: +39 02 665241, Fax: +39 02 66501492 • Study coordinator: Gabriele Camattari • Global Head Medical Affairs CNS: Carlo Cattaneo • EU Qualified Person Responsible for Pharmacovigilance: Maria Luisa Bonura *For Contract Research Organization*: MediNeos, Viale Virgilio 54/U, 41123 Modena (Italy), Phone: +39 059 88.60.134, Fax: +39 059 84.83.05 • Study coordinator: Alessandra Ori • Statistician: Lucia Simoni

Marketing authorisation holder(s)

Marketing authorisation holder(s)	Zambon S.p.A. - Via Lillo del Duca, 10, 20091 - Bresso (MI), Italy
MAH contact person	Marzia Michieletto – Zambon S.p.A.

Table of contents

1. Abstract

Title

European multicenter retrospective-prospective cohort study to observe Safinamide safety profile and pattern of use in clinical practice during the first post-commercialization phase – Study Z7219N02

Keywords

Safinamide

Parkinson's Disease

Elderly patients

Patients with comorbidities

Rationale and background

Safinamide is an α-aminoamide indicated as add-on therapy for the treatment of patients with idiopathic PD, in mid- to late-stage fluctuating patients receiving a stable dose of levodopa (L-dopa) alone or in combination with other PD medications. In pivotal trials, safinamide 50 mg/day and 100 mg/day increased total daily "on" time with no or non-troublesome dyskinesia [3, 4, 10].

Research question and objectives

During the initial marketing authorization procedure, the European Medicines Agency (EMA) recommended that Zambon provide additional real world data on safinamide given the uncertainties regarding categories of patients not well represented in clinical trials, namely patients aged > 75 and those with concomitant psychiatric conditions. Following this request, a Drug Utilization Study (DUS) on safinamide in routine clinical practice was designed.

Primary objective:

To describe the occurrence of adverse events in patients treated with safinamide in real-life conditions during one year in the first post-commercialization phase as reported by the Investigators.

The analysis was conducted overall and in the targeted subgroups, namely in patients aged >75, those with relevant comorbidities and those with psychiatric conditions.

Secondary objectives:

1. To describe the characteristics of patients treated with safinamide according to clinical practice.
2. To describe safinamide treatment patterns in real-life settings.

Study design

Multi-country multicentre retrospective-prospective cohort observational study. The study lasted 34 months, including a 22-month enrolment period and 12-month follow-up period.

Setting

This is a drug-utilization study collecting data from real-world clinical practice. The countries involved were Belgium, Germany, Italy, Spain, Switzerland and United Kingdom.

Subjects

Adults patients (≥18 years) who started treatment with safinamide at enrolment visit or who started it in the previous four months according to clinical practice, with signed informed and privacy consent form. Patients were excluded if they were participating in any clinical trial on safinamide at study inclusion.

In Germany, only patients with confirmed diagnosis of idiopathic Parkinson's disease who presented administration of safinamide in accordance with the local SmPC were included, as per local Health Authority requirement on local regulations.

Study size

A total of 1600 patients were expected to be enrolled in the study. Sample size was defined based on feasibility considerations concerning the length of the enrolment period and site capacity. In total, 128 sites enrolled 1610 patients.

Variables and Data sources

For all patients enrolled in the study after the signature of the Informed Consent, data were recorded on the Study electronic Case Report Form (eCRF) by the Investigator, both by retrieving already available data from the medical charts and by interviewing the patient, in order to collect information that, as per single centre practice, would not be reported in the patient's medical chart.

The Investigator was asked to report all the AEs (serious or otherwise, related or not to safinamide) and pregnancy cases occurred during the observation period of which he/she became aware.

Data analysis

The analyses were provided overall and by subgroups of interest, namely patients aged >75, those concomitantly suffering from relevant comorbidities and those with psychiatric conditions.

The aim of the study is merely descriptive and there are no pre-specified hypotheses.

Results

Out of 1610 enrolled patients, 1558 (96.8%) were evaluable for the analysis, 1326 (82.4%) patients were evaluable at 12-month follow-up visit. Males were 961 (61.7%), mean (SD) age at enrollment was 68.4 (9.7) and 1543 (99%) patients were Caucasian.

The sub-groups of special interest were: 391 (25.1%) patients aged over 75, 1103 (70.8%) patients with relevant comorbidities and 661 (42.4%) patients with psychiatric conditions.

Safinamide was administered with an initial dose of 50 mg/die for 1452 (93.2%) patients, and in total 336 discontinuations were observed for 21.6% of patients. Almost half of the discontinuations occurred due to adverse reaction (N=161, 47.9%).

During observation 714 (45.8%) patients experienced in total 1435 AEs and 432 (27.7%) patients experienced in total 685 ADRs; 143 patients (9.2%) had SAEs during observation and 36 patients (2.3%) SADRs. The total number of SAEs and SADRs were 194 and 48, respectively. Adverse events were mainly mild (N=888, 61.9%). One third of occurred events (N=480; 33.4%) were nervous system disorders and 14.3% (N=205) were psychiatric disorders. Among nervous system disorders, the most frequently reported AEs were dyskinesia (N=197, 13.7%) and dizziness (N=39, 2.7%), while among psychiatric disorders, hallucinations were the most frequently reported (N=41, 2.9%). No causal relation with safinamide was reported for 750 (52.3%) events, while 29 (2.0%) events had a definite relation with safinamide (among which 8 dyskinesias, 2 hallucinations, 2 agitation, 2 muscle rigidity). Eye disorders with possible and probable relation with safinamide were 14 (1.0%) and 7 (0.5%) events, respectively. For 993 AEs (69.2%) no action was taken. The outcome of the 1435 occurred adverse events was recovered/resolved in 824 (57.4%) events.

The most frequently reported SAEs were infections (N=38, 2.6%; pneumonia, urinary tract infections, lung infections, respiratory tract infections), fractures (N=31, 2.2%) and nervous system disorders (N=29, 2.0%; dyskinesias, cerebrovascular accidents and parkinsonisms).

Elderly patients

During observation 185 (47.3%) patients older than 75 had at least one AE (total number of AEs: 370) and 102 patients (26.1%) had at least one ADR (total number of ADRs: 155); 53 (13.6%) patients experienced 74 SAE and 9 patients (2.3%) 11 SADR.

The proportion of events not related with safinamide was higher in patients aged >75 (N=215, 58.1%) than in patients aged ≤75 (N=535, 50.2%).

For 255 AEs (68.9%), in patients older than 75, no actions were taken, instead drug was permanently interrupted in 83 (22.4%) adverse events. In patients older than 75, 221 (59.7%) events were recovered/resolved.

Patients with comorbidities
During observation 542 (49.1%) patients with relevant comorbidities had a total of 1151 AEs and 315 patients (28.6%) had 517 ADRs; 122 (11.1%) patients had at least one SAE and 28 patients (2.5%) at least one SADR. The total number of SAEs and SADRs in this subpopulation were 169 and 40, respectively. It can be noticed that the proportion of patients with AEs and SAEs was lower in patients without relevant comorbidities (N=172, 37.8% and N=21, 4.6% respectively) than in patients with relevant comorbidities. The proportion of events not related with safinamide was higher in patients with relevant comorbidities (N=634, 55.1% of total number of occurred events in this sub group) than in patients without relevant comorbidities (N=116, 40.8%).

Patients with psychiatric conditions
Patients with psychiatric conditions experienced 653 AEs in 316 cases (47.8%), similar to patients without psychiatric conditions (782 AEs in 398 cases, 44.4%). In patients with psychiatric conditions the frequency of severe events (N=69, 10.6%) was similar to the one observed in patients without psychiatric conditions (N=74, 9.5%); for 430 AEs (65.8%) no action was taken. Patients with and without psychiatric conditions had dyskinesia in 92 (13.9%) and 91 (10.1%) cases, respectively.

Discussion
The SYNAPSES study confirms the good safety profile of safinamide even in special groups of patients, namely patients aged≥ 75, patients with comorbidities and with psychiatric conditions. Neither age, comorbidities, nor psychiatric conditions seem to have any relevant effect on the safety profile of safinamide.

Marketing Authorisation Holder(s)

Marketing authorisation holder(s)	Zambon S.p.A. - Via Lillo del Duca, 10, 20091 - Bresso (MI), Italy
MAH contact person	Marzia Michieletto – Zambon S.p.A.

Names and affiliations of principal investigators

Country	Site code	PI	Institution	City
Italy	301	Prof. Carmine Marini	P.O. San Salvatore - Centro Sclerosi Multipla Clinica Neurologica	L'Aquila
Italy	302	Dr. Carmine Vitale	IDC Capodimonte – Neurologia	Napoli
Italy	303	Prof. Alessandro Tessitore	A.O.U. Seconda Università di Napoli - I Clinica Neurologica	Napoli
Italy	304	Prof. Paolo Barone	A.O.U. OO.RR. S.Giovanni di Dio e Ruggi D'Aragona – Neurologia	Salerno
Italy	305	Dr. Anna Negrotti	Azienda Ospedaliera Universitaria - Neurologia	Parma
Italy	306	Dr. Mariachiara Sensi	Arcispedale Sant'Anna – Neurologia	Cona

Country	Site code	PI	Institution	City
Italy	307	Dr. Pietro Cortelli	Ospedale Bellaria – Neurologia	Bologna
Italy	308	Dr. Sara Contardi	Nuovo Ospedale Sant'Agostino-Estense - Clinica Neurologica	Modena
Italy	309	Dr. Enrico Belgrado	A.O.U. S.Maria della Misericordia - SOC Neurologia	Udine
Italy	310	Dr. M.Francesca De Pandis	Ospedale San Raffaele Cassino - U.O. Riabilitazione Neuromotoria	Cassino
Italy	311	Dr. Anna Rita Bentivoglio	Università Cattolica S. Cuore Policlinico Gemelli – Neurologia	Roma
Italy	312	Prof. Vincenzo Di Lazzaro	Università Campus Bio-Medico – Neurologia	Roma
Italy	313	Prof. Francesco E. Pontieri	A.O. Sant' Andrea - Univ. La Sapienza - U.O.C. Neurologia	Roma
Italy	314	Prof. Giovanni Fabbrini	Policlinico Umberto I - Univ La Sapienza - Neurologia B - Dip. Scienze Neurologiche	Roma
Italy	315	Dr. Alessandra Monge	Ospedale San Giovanni Battista – Neurologia	Roma
Italy	316	Prof. Alessandro Stefani	Policlinico Tor Vergata - Clinica Neurologica	Roma
Italy	317	Prof. Giovanni Abbruzzese	Università degli Studi di Genova - Centro Parkinson - Dipartimento DINOGMI	Genova
Italy	318	Dr. Anna Lena Zecchinelli	ASST Gaetano Pini-CTO - Centro per la malattia di Parkinson e disturbi del movimento	Milano
Italy	319	Dr. M. Antonietta Volontè	Ospedale San Raffaele - Dipartimento Neurologico	Milano
Italy	320	Prof. Alessandro Padovani	ASST Spedali Civili - U.O. 2^ Neurologia	Brescia
Italy	321	Prof. Alberto Priori	ASST Santi Paolo e Carlo – Neurologia	Milano
Italy	322	Dr. Claudio Pacchetti	Istituto Neurologico C. Mondino - U.O. Parkinson	Pavia
Italy	324	Dr. Roberto Baruffaldi	A.O.U. Ospedali Riuniti - Clinica Neurologia	Ancona

Country	Site code	PI	Institution	City
Italy	325	Prof. Marco Onofrj	Fondazione Univ. D'Annunzio - Centro Ricerche Cliniche	Chieti
Italy	326	Prof. Diego Centonze	Istituto Neurologico Mediterraneo Neuromed – Neurologia	Pozzilli
Italy	327	Prof. Leonardo Lopiano	A.S.O. Molinette - Neurologia 2	Torino
Italy	328	Prof. Marco Aguggia	Ospedale Cardinal Massaia – Neurologia	Asti
Italy	329	Dr. Filippo Tamma	Ospedale Generale Regionale F.Miulli - U.O.C. Neurologia	Acquaviva delle Fonti
Italy	330	Dr. Giovanni Iliceto	A.O.U. Policlinico Consorziale - U.O. Neurofisiopatologia	Bari
Italy	331	Dr. Giovanni Cossu	Azienda Ospedaliera G. Brotzu - U.O. Neurologia	Cagliari
Italy	332	Dr. Antonino Cannas	A.O.U. Policlinico Monserrato – Neurologia	Monserrato
Italy	333	Dr. Tania Avarello	A.O Riuniti Villa Sofia-Cervello - Neurologia Centro Rif.Regionale Parkinson	Palermo
Italy	334	Prof. Mario Zappia	A.O.U. Policlinico-Vittorio Emanuele - Clinica Neurologica	Catania
Italy	335	Dr. Francesca Morgante	A.O.U. Policlinico G. Martino - UOSD Neurofisiopatologia e Disordini del Movimento	Messina
Italy	336	Dr. Roberto Marconi	Ospedale della Misericordia – Neurologia	Grosseto
Italy	337	Dr. Roberto Ceravolo	A.O.U. Pisana Ospedale Santa Chiara - U.O. Neurologia	Pisa
Italy	338	Prof. Paolo Calabresi	Ospedale S. Maria della Misericordia - Clinica Neurologica	Perugia
Italy	339	Dr. Elisabetta Gasparoli	Ospedale San Camillo - U.O. Malattia di Parkinson	Venezia Lido
Italy	340	Dr. Rocco Quatrale	Ospedale dell'Angelo – Neurologia	Mestre
Italy	341	Dr. Giampietro Nordera	Casa di Cura Villa Margherita – Neurologia	Arcugnano
Italy	342	Prof. Michele Tinazzi	Policlinico - Borgo Roma - U.O. Neurologia B	Verona

Country	Site code	PI	Institution	City
Italy	343	Dr. Marco Guidi	Ospedale San Salvatore – Neurologia	Pesaro
Italy	344	Dr. Marco D'Amelio	A.O.U. Policlinico P. Giaccone – Neurologia	Palermo
Italy	345	Dr. Massimo Moleri	Casa di Cura San Francesco – Neurologia	Bergamo
Italy	346	Dr. Claudio Callegarini	Ospedale civile S.Maria delle Croci – Neurologia	Ravenna
Italy	347	Dr. Domenico Bosco	Ospedale S. Giovanni di Dio – Neurologia	Crotone
Italy	348	Prof. Paolo Manganotti	Azienda Ospedaliera Universitaria Integrata – Neurologia	Trieste
Italy	349	Dr. Cristoforo Comi	A.O.U. Maggiore della Carità – Neurologia	Novara
Italy	350	Dr. Marco Mauri	Ospedale di Circolo e Fondazione Macchi – Neurologia	Varese
Italy	351	Dr. Sandro Zambito Marsala	Ospedale San Martino – Neurologia	Belluno
Italy	352	Prof. Carlo Colosimo	A.O. Santa Maria - U.O.C. Neurologia	Terni
Italy	355	Prof. Alessandro Denaro	Istituto Chirurgico Ortopedico Traumatologico - Riabilitazione Neurologica	Latina
Spain	401	Dr. Juan José López Lozano	Hospital Puerta de Hierro	Majadahonda
Spain	402	Dr. Juan Carlos Gómez Esteban	Hospital de Cruces	Barakaldo
Spain	403	Dr. Mari Cruz Rodríguez Oroz	Hospital de Donostia	Donostia
Spain	404	Dr. Juan Carlos Martinez Castrillo	Hospital Ramón y Cajal	Madrid
Spain	405	Dr. José Matías Arbelo Gonzalez	Hospital Insular de Las Palmas	Las Palmas
Spain	406	Dr. Diego Santos García	Hospital Arquitecto Marcide	El Ferrol
Spain	407	Dr. Jose Manuel García Moreno	Hospital Universitario Virgen Macarena	Sevilla
Spain	408	Dr. Matilde Calopa Garriga	Hospital Universitari de Bellvitge	L'Hospitalet de Llobregat
Spain	409	Dr. Raúl Espinosa Rosso	Hospital Univeritario Puerta del Mar	Cadiz
Spain	410	Dr. Lydia López Manzanares	Hospital Univeritario La Princesa	Madrid

Country	Site code	PI	Institution	City
Spain	412	Dr. Víctor Campos Arillo	Xanit Hospital Internacional	Benalmádena
Spain	413	Dr. Julia Vaamonde Gamo	Hospital General Universitario de Ciudad Real	Ciudad Real
Spain	414	Dr. Oriol de Fábregues	Hospital Universitari Vall d'Hebron	Barcelona
Spain	415	Dr. Angels Bayés	Hospital Quirón-Teknon	Barcelona
Spain	416	Dr. Inés Legarda	Hospital Universitari Son Espases	Palma de Mallorca
Spain	417	Dr. Juan Juni	Fundación Investigación Hospital General Universitario de Valencia	Valencia
Spain	418	Dr. Irene Martínez	Hospital Universitari i Politècnic La Fe	Valencia
Spain	419	Dr. Carlos Leiva	Hospital General Universitario de Alicante	Alicante
Spain	420	Dr. Elvira García Cobos	Hospital Público Universitario Del Henares	Coslada (Madrid)
Spain	421	Dr. Sonia Escalante Arroyo	Hospital de Tortosa Verge de la Cinta	Tortosa
Spain	422	Dr. Eric Freire	Hospital General Universitario de Elche	Elche
Spain	423	Dr. Jaime Kulisevsky	Hospital de la Santa Creu i Sant Pau	Barcelona
Spain	424	Dr. Mónica Kurtis	Ruber Internacional	Madrid
Spain	425	Dr. Esther Cubo	Hospital Universitario de Burgos	Burgos
Spain	426	Dr. Núria López Aristegui	Hospital Virgen de la Salud	Toledo
Spain	428	Dr. Maria Jose Martí Domenech	Clínic Universitari Barcelona	Barcelona
Spain	429	Dr. Sara Sanchez	Hospital Lozano Blesa	Zaragoza
Spain	430	Dr. Maria Rosario Luquín	Clínica Universidad de Navarra	Pamplona
Spain	431	Dr. Berta Pascual Sedano	Hospital Dexeus	Barcelona
Spain	432	Dr. Francisco Grandas Perez	Hospital Gregorio Marañon	Madrid
Spain	433	Dr. Pablo Mir Rivera	Hospital Virgen del Rocío	Sevilla
Spain	435	Dr. Marina Mata	Hospital Universitario Infanta Sofía	Madrid
Spain	436	Dr. Alberto Esquivel López	Hospital Universitario Infanta Leonor	Madrid

Country	Site code	PI	Institution	City
Spain	437	Dr. Jessica González-Ardura	Hospital Universitario Locus Augusti de Lugo	Lugo
Spain	438	Dr. Marta Blazquez	Hospital Universitario Central de Asturias	Oviedo
Spain	440	Dr. Juan José Rodríguez Uranga	Centro de Neurología Avanzada	Sevilla
Spain	441	Dr. Berta Solano	Hospital Santa Caterina	Salt - Girona
Spain	443	Dr. Antoni Callen	Hospital Parc Sanitari Sant Joan	Sant Boi de Llobregat
Germany	201	PD. Dr. med. Bernhard Hellwig	Gemeinschaftspraxis für Neurologie, Psychiatrie und Psychotherapie Dres. Gerlach und Kollegen	Freiburg
Germany	202	Dr. med. Heinz-Peter Herbst	Neurozentrum Stuttgart Mitte	Stuttgart
Germany	204	Prof. Dr. med. Siegfried Muhlack	Katholisches Klinikum Bochum gGmbH Neurologische Klinik	Bochum
Germany	205	Prof. Dr. med. Andreas Kupsch	Neurologie Bewegt Ärztehaus BISMARCK KARREE	Berlin
Germany	206	Dr. med. Michael Lang	Nervenärztliche Gemeinschaftspraxis NeuroPoint GmbH	Ulm
Germany	207	Dr. med. Martin Delf	Gesundheitszentrum Hoppegarten Praxis für Neurologie	Hoppegarten
Germany	210	Prof. Dr. med. Dirk Woitalla	St. Josef-Krankenhaus Kupferdreh Neurologie	Essen
Germany	211	Prof. Dr. med. Johannes Schwarz	Kliniken Kreis Mühldorf am Inn, Parkinson und andere Bewegungsstörungen, Abteilung f. klinische Studien	Haag i. OB
Germany	214	Dr. med. Christian Oehlwein	Praxis für Psychiatrie und Neurologie	Gera
Germany	215	Prof. Dr. med. Tobias Warnecke	Universitätsklinikum Münster, Klinik für Allgemeine Neurologie	Münster
Germany	216	Prof. Dr. med. Wolfgang Jost	Parkinson-Klinik Ortenau GmbH & Co. KG, Zentrum für neurologische Bewegungsstörungen	Wolfach
Germany	217	Dr. med. Wendelin Kyrill Blersch	Praxis für Neurologie	Regensburg
Germany	218	Dr. Eugen Schlegel	Neurologische Praxis Siegen	Siegen

Country	Site code	PI	Institution	City
Germany	221	Dr. med. Ilias Nastos	Neurologische Facharztpraxis	Bochum
Belgium	101	Prof. Dr. Patrick Cras	Universitair Ziekenhuis Antwerpen	Edegem (Antwerp)
Belgium	102	Prof. Dr. Gaëtan Garraux	Centre Hospitalier Universitaire Sart Tilman	Liège
Belgium	103	Prof. Dr. Patrick Santens	Universitair Ziekenhuis Gent	Gent
Belgium	104	Prof. Dr. Anne Jeanjean	Hôpital Saint-Luc	Louvain (Brussels)
Belgium	105	Prof. Dr. Frédéric Supiot	Hôpital Erasme	Brussels
Belgium	106	Dr. Philip Bourgeois	AZ Delta campus Wilgenstraat	Roeselare
Belgium	107	Prof. Dr. Sophie Dethy	CHU Tivoli	La Louvière
Belgium	108	Dr. Bruno Bergmans	AZ Sint-Jan	Brugge
Belgium	109	Dr. Chris Van der Linden	Sint Lucas Ziekenhuis	Gent
Belgium	110	Dr. De Klippel	Virga Jesse Ziekenhuis	Hasselt
Belgium	111	Dr Karine Geens	Algemeen Ziekenhuis Klina	Antwerp
Belgium	112	Dr Philippe Jacquerye	Clinique St. Pierre	Ottignies
Belgium	113	Dr Gianni Franco	CHU UCL Namur	Dinant
UK	603	Dr. Emily Henderson	Royal United Hospitals Bath NHS Foundation Trust	Bath
UK	610	Dr. Monty Silverdale	Greater Manchester Neuroscience Centre, Salford Royal NHS Foundation Trust	Salford
UK	614	Dr. Camille Carroll (CI)	Livewell Southwest / Royal Devon & Exeter NHS Foundation Trust	Plymouth
UK	625	Dr. Jason Raw	Fairfield General Hospital, Ward 19 Clinical Trials Unit	Bury
UK	626	Dr. Sandip Raha	Princess of Wales Hospital	Wales
UK	628	Dr. Nishthana Silva	Kings Mill hospital	Mansfield
Switzerland	501	Prof. Dr. med. Stephan Bohlhalter	Luzerner Kantonsspital Neurology and Neuroabilitation	Lucerne
Switzerland	502	Dr. Joan Michelis	Inselspital Universitätsklinik für Neurologie	Bern
Switzerland	503	PD. Dr. med. Georg Kägi	Kantonsspital St. Gallen Neurology Clinic	St.Gallen
Switzerland	504	Prof. Dr. med. Alain Kälin	Ospedale Civico, Neurocentro della Svizzera Italiana	Lugano

Country	Site code	PI	Institution	City
Switzerland	506	Dr Ettore Accolla	Kantonsspital Fribourg Service de neurologie	Fribourg

2. List of abbreviations

ADL	Activities of Daily Living
ADR	Adverse Drug Reaction
AE	Adverse Event
AES	Apathy Evaluation Scale
AESI	Adverse Event of Special Interest
ATC	Anatomical Therapeutic Chemical
BS	Biostatistician
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte
CDM	Clinical Data Manager
CGI	Clinical global impression
CI	Confidence Interval
COMT	Catechol-O-methyltransferase
DUS	Drug Utilization Study
eCRF	electronic Case Report Form
EMA	European Medicines Agency
EU	European
FAS	Full Analysis Set
GAMP	Good Automated Manufacturing Practice
GPP	Good Pharmacoepidemiology Practice
H&Y	Hoehn & Yahr stage
IT	Information Technology
L-dopa	Levodopa
MAO-B	Mono-Amine Oxidase type B
MDS	Movement Disorder Society
MedDRA	Medical Dictionary for Regulatory Activities
NA	Not Applicable / Not Available
NMS	Non-Motor Symptoms
PD	Parkinson’s Disease
PDQ-39	Parkinson's Disease Questionnaire – 39 items
PT	Preferred Term
REM	Rapid Eye Movement
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SNRI	Serotonin–Norepinephrine Reuptake Inhibitors
SOC	System Organ Class

SSRI	Selective Serotonin Reuptake Inhibitors
TEAE	Treatment Emergent Adverse Event
UPDRS	Unified Parkinson's Disease Rating Scale
US	United States

3. Investigators

[List of name and affiliation of the principal investigator, a coordinating investigator for each country in which the study is to be performed and investigators in other relevant study sites. Contact details and the list of all investigators can be kept in a stand-alone document to be listed in Annex 1 and to be provided upon request.]

Country	Site code	PI	Institution	City
Italy	301	Prof. Carmine Marini	P.O. San Salvatore - Centro Sclerosi Multipla Clinica Neurologica	L'Aquila
Italy	302	Dr. Carmine Vitale	IDC Capodimonte – Neurologia	Napoli
Italy	303	Prof. Alessandro Tessitore	A.O.U. Seconda Università di Napoli - I Clinica Neurologica	Napoli
Italy	304	Prof. Paolo Barone	A.O.U. OO.RR. S.Giovanni di Dio e Ruggi D'Aragona – Neurologia	Salerno
Italy	305	Dr. Anna Negrotti	Azienda Ospedaliera Universitaria - Neurologia	Parma
Italy	306	Dr. Mariachiara Sensi	Arcispedale Sant'Anna – Neurologia	Cona
Italy	307	Dr. Pietro Cortelli	Ospedale Bellaria – Neurologia	Bologna
Italy	308	Dr. Sara Contardi	Nuovo Ospedale Sant'Agostino-Estense - Clinica Neurologica	Modena
Italy	309	Dr. Enrico Belgrado	A.O.U. S.Maria della Misericordia - SOC Neurologia	Udine
Italy	310	Dr. M.Francesca De Pandis	Ospedale San Raffaele Cassino - U.O. Riabilitazione Neuromotoria	Cassino
Italy	311	Dr. Anna Rita Bentivoglio	Università Cattolica S. Cuore Policlinico Gemelli – Neurologia	Roma
Italy	312	Prof. Vincenzo Di Lazzaro	Università Campus Bio-Medico – Neurologia	Roma
Italy	313	Prof. Francesco E. Pontieri	A.O. Sant' Andrea - Univ. La Sapienza - U.O.C. Neurologia	Roma
Italy	314	Prof. Giovanni Fabbrini	Policlinico Umberto I - Univ La Sapienza - Neurologia B - Dip. Scienze Neurologiche	Roma
Italy	315	Dr. Alessandra Monge	Ospedale San Giovanni	Roma

			Battista – Neurologia	
Italy	316	Prof. Alessandro Stefani	Policlinico Tor Vergata - Clinica Neurologica	Roma
Italy	317	Prof. Giovanni Abbruzzese	Università degli Studi di Genova - Centro Parkinson - Dipartimento DINOGMI	Genova
Italy	318	Dr. Anna Lena Zecchinelli	ASST Gaetano Pini-CTO - Centro per la malattia di Parkinson e disturbi del movimento	Milano
Italy	319	Dr. M. Antonietta Volontè	Ospedale San Raffaele - Dipartimento Neurologico	Milano
Italy	320	Prof. Alessandro Padovani	ASST Spedali Civili - U.O. 2^ Neurologia	Brescia
Italy	321	Prof. Alberto Priori	ASST Santi Paolo e Carlo – Neurologia	Milano
Italy	322	Dr. Claudio Pacchetti	Istituto Neurologico C. Mondino - U.O. Parkinson	Pavia
Italy	324	Dr. Roberto Baruffaldi	A.O.U. Ospedali Riuniti - Clinica Neurologia	Ancona
Italy	325	Prof. Marco Onofrj	Fondazione Univ. D'Annunzio - Centro Ricerche Cliniche	Chieti
Italy	326	Prof. Diego Centonze	Istituto Neurologico Mediterraneo Neuromed – Neurologia	Pozzilli
Italy	327	Prof. Leonardo Lopiano	A.S.O. Molinette - Neurologia 2	Torino
Italy	328	Prof. Marco Aguggia	Ospedale Cardinal Massaia – Neurologia	Asti
Italy	329	Dr. Filippo Tamma	Ospedale Generale Regionale F.Miulli - U.O.C. Neurologia	Acquaviva delle Fonti
Italy	330	Dr. Giovanni Iliceto	A.O.U. Policlinico Consorziale - U.O. Neurofisiopatologia	Bari
Italy	331	Dr. Giovanni Cossu	Azienda Ospedaliera G. Brotzu - U.O. Neurologia	Cagliari
Italy	332	Dr. Antonino Cannas	A.O.U. Policlinico Monserrato – Neurologia	Monserrato
Italy	333	Dr. Tania Avarello	A.O Riuniti Villa Sofia-Cervello - Neurologia Centro Rif.Regionale Parkinson	Palermo
Italy	334	Prof. Mario Zappia	A.O.U. Policlinico-Vittorio Emanuele - Clinica Neurologica	Catania
Italy	335	Dr. Francesca	A.O.U. Policlinico G.	Messina

		Morgante	Martino - UOSD Neurofisiopatologia e Disordini del Movimento	
Italy	336	Dr. Roberto Marconi	Ospedale della Misericordia – Neurologia	Grosseto
Italy	337	Dr. Roberto Ceravolo	A.O.U. Pisana Ospedale Santa Chiara - U.O. Neurologia	Pisa
Italy	338	Prof. Paolo Calabresi	Ospedale S. Maria della Misericordia - Clinica Neurologica	Perugia
Italy	339	Dr. Elisabetta Gasparoli	Ospedale San Camillo - U.O. Malattia di Parkinson	Venezia Lido
Italy	340	Dr. Rocco Quatrale	Ospedale dell'Angelo – Neurologia	Mestre
Italy	341	Dr. Giampietro Nordera	Casa di Cura Villa Margherita – Neurologia	Arcugnano
Italy	342	Prof. Michele Tinazzi	Policlinico - Borgo Roma - U.O. Neurologia B	Verona
Italy	343	Dr. Marco Guidi	Ospedale San Salvatore – Neurologia	Pesaro
Italy	344	Dr. Marco D'Amelio	A.O.U. Policlinico P. Giaccone – Neurologia	Palermo
Italy	345	Dr. Massimo Moleri	Casa di Cura San Francesco – Neurologia	Bergamo
Italy	346	Dr. Claudio Callegarini	Ospedale civile S.Maria delle Croci – Neurologia	Ravenna
Italy	347	Dr. Domenico Bosco	Ospedale S. Giovanni di Dio – Neurologia	Crotone
Italy	348	Prof. Paolo Manganotti	Azienda Ospedaliera Universitaria Integrata – Neurologia	Trieste
Italy	349	Dr. Cristoforo Comi	A.O.U. Maggiore della Carità – Neurologia	Novara
Italy	350	Dr. Marco Mauri	Ospedale di Circolo e Fondazione Macchi – Neurologia	Varese
Italy	351	Dr. Sandro Zambito Marsala	Ospedale San Martino – Neurologia	Belluno
Italy	352	Prof. Carlo Colosimo	A.O. Santa Maria - U.O.C. Neurologia	Terni
Italy	355	Prof. Alessandro Denaro	Istituto Chirurgico Ortopedico Traumatologico - Riabilitazione Neurologica	Latina
Spain	401	Dr. Juan José López Lozano	Hospital Puerta de Hierro	Majadahonda
Spain	402	Dr. Juan Carlos Gómez Esteban	Hospital de Cruces	Barakaldo

Spain	403	Dr. Mari Cruz Rodríguez Oroz	Hospital de Donostia	Donostia
Spain	404	Dr. Juan Carlos Martinez Castrillo	Hospital Ramón y Cajal	Madrid
Spain	405	Dr. José Matías Arbelo Gonzalez	Hospital Insular de Las Palmas	Las Palmas
Spain	406	Dr. Diego Santos García	Hospital Arquitecto Marcide	El Ferrol
Spain	407	Dr. Jose Manuel García Moreno	Hospital Universitario Virgen Macarena	Sevilla
Spain	408	Dr. Matilde Calopa Garriga	Hospital Universitari de Bellvitge	L'Hospitalet de Llobregat
Spain	409	Dr. Raúl Espinosa Rosso	Hospital Univeritario Puerta del Mar	Cadiz
Spain	410	Dr. Lydia López Manzanares	Hospital Univeritario La Princesa	Madrid
Spain	412	Dr. Víctor Campos Arillo	Xanit Hospital Internacional	Benalmádena
Spain	413	Dr. Julia Vaamonde Gamo	Hospital General Universitario de Ciudad Real	Ciudad Real
Spain	414	Dr. Oriol de Fábregues	Hospital Universitari Vall d'Hebron	Barcelona
Spain	415	Dr. Angels Bayés	Hospital Quirón-Teknon	Barcelona
Spain	416	Dr. Inés Legarda	Hospital Universitari Son Espases	Palma de Mallorca
Spain	417	Dr. Juan Juni	Fundación Investigación Hospital General Universitario de Valencia	Valencia
Spain	418	Dr. Irene Martínez	Hospital Universitari i Politècnic La Fe	Valencia
Spain	419	Dr. Carlos Leiva	Hospital General Universitario de Alicante	Alicante
Spain	420	Dr. Elvira García Cobos	Hospital Público Universitario Del Henares	Coslada (Madrid)
Spain	421	Dr. Sonia Escalante Arroyo	Hospital de Tortosa Verge de la Cinta	Tortosa
Spain	422	Dr. Eric Freire	Hospital General Universitario de Elche	Elche
Spain	423	Dr. Jaime Kulisevsky	Hospital de la Santa Creu i Sant Pau	Barcelona
Spain	424	Dr. Mónica Kurtis	Ruber Internacional	Madrid
Spain	425	Dr. Esther Cubo	Hospital Universitario de Burgos	Burgos

Spain	426	Dr. Núria López Aristegui	Hospital Virgen de la Salud	Toledo
Spain	428	Dr. Maria Jose Martí Domenech	Clínic Universitari Barcelona	Barcelona
Spain	429	Dr. Sara Sanchez	Hospital Lozano Blesa	Zaragoza
Spain	430	Dr. Maria Rosario Luquín	Clínica Universidad de Navarra	Pamplona
Spain	431	Dr. Berta Pascual Sedano	Hospital Dexeus	Barcelona
Spain	432	Dr. Francisco Grandas Perez	Hospital Gregorio Marañon	Madrid
Spain	433	Dr. Pablo Mir Rivera	Hospital Virgen del Rocío	Sevilla
Spain	435	Dr. Marina Mata	Hospital Universitario Infanta Sofía	Madrid
Spain	436	Dr. Alberto Esquivel López	Hospital Universitario Infanta Leonor	Madrid
Spain	437	Dr. Jessica González-Ardura	Hospital Universitario Locus Augusti de Lugo	Lugo
Spain	438	Dr. Marta Blazquez	Hospital Universitario Central de Asturias	Oviedo
Spain	440	Dr. Juan José Rodríguez Uranga	Centro de Neurología Avanzada	Sevilla
Spain	441	Dr. Berta Solano	Hospital Santa Caterina	Salt - Girona
Spain	443	Dr. Antoni Callen	Hospital Parc Sanitari Sant Joan	Sant Boi de Llobregat
Germany	201	PD. Dr. med. Bernhard Hellwig	Gemeinschaftspraxis für Neurologie, Psychiatrie und Psychotherapie Dres. Gerlach und Kollegen	Freiburg
Germany	202	Dr. med. Heinz-Peter Herbst	Neurozentrum Stuttgart Mitte	Stuttgart
Germany	204	Prof. Dr. med. Siegfried Muhlack	Katholisches Klinikum Bochum gGmbH Neurologische Klinik	Bochum
Germany	205	Prof. Dr. med. Andreas Kupsch	Neurologie Bewegt Ärztehaus BISMARCK KARREE	Berlin
Germany	206	Dr. med. Michael Lang	Nervenärztliche Gemeinschaftspraxis NeuroPoint GmbH	Ulm
Germany	207	Dr. med. Martin Delf	Gesundheitszentrum Hoppegarten Praxis für Neurologie	Hoppegarten
Germany	210	Prof. Dr. med. Dirk Woitalla	St. Josef-Krankenhaus Kupferdreh Neurologie	Essen
Germany	211	Prof. Dr. med. Johannes Schwarz	Kliniken Kreis Mühldorf am Inn, Parkinson und andere Bewegungsstörungen,	Haag i. OB

			Abteilung f. klinische Studien	
Germany	214	Dr. med. Christian Oehlwein	Praxis für Psychiatrie und Neurologie	Gera
Germany	215	Prof. Dr. med. Tobias Warnecke	Universitätsklinikum Münster, Klinik für Allgemeine Neurologie	Münster
Germany	216	Prof. Dr. med. Wolfgang Jost	Parkinson-Klinik Ortenau GmbH & Co. KG, Zentrum für neurologische Bewegungsstörungen	Wolfach
Germany	217	Dr. med. Wendelin Kyrill Blersch	Praxis für Neurologie	Regensburg
Germany	218	Dr. Eugen Schlegel	Neurologische Praxis Siegen	Siegen
Germany	221	Dr. med. Ilias Nastos	Neurologische Facharztpraxis	Bochum
Belgium	101	Prof. Dr. Patrick Cras	Universitair Ziekenhuis Antwerpen	Edegem (Antwerp)
Belgium	102	Prof. Dr. Gaëtan Garraux	Centre Hospitalier Universitaire Sart Tilman	Liège
Belgium	103	Prof. Dr. Patrick Santens	Universitair Ziekenhuis Gent	Gent
Belgium	104	Prof. Dr. Anne Jeanjean	Hôpital Saint-Luc	Louvain (Brussels)
Belgium	105	Prof. Dr. Frédéric Supiot	Hôpital Erasme	Brussels
Belgium	106	Dr. Philip Bourgeois	AZ Delta campus Wilgenstraat	Roeselare
Belgium	107	Prof. Dr. Sophie Dethy	CHU Tivoli	La Louvière
Belgium	108	Dr. Bruno Bergmans	AZ Sint-Jan	Brugge
Belgium	109	Dr. Chris Van der Linden	Sint Lucas Ziekenhuis	Gent
Belgium	110	Dr. De Klippel	Virga Jesse Ziekenhuis	Hasselt
Belgium	111	Dr Karine Geens	Algemeen Ziekenhuis Klina	Antwerp
Belgium	112	Dr Philippe Jacquerye	Clinique St. Pierre	Ottignies
Belgium	113	Dr Gianni Franco	CHU UCL Namur	Dinant
UK	603	Dr. Emily Henderson	Royal United Hospitals Bath NHS Foundation Trust	Bath
UK	610	Dr. Monty Silverdale	Greater Manchester Neuroscience Centre, Salford Royal NHS Foundation Trust	Salford
UK	614	Dr. Camille Carroll (CI)	Livewell Southwest / Royal Devon & Exeter NHS Foundation Trust	Plymouth
UK	625	Dr. Jason Raw	Fairfield General Hospital, Ward 19 Clinical Trials Unit	Bury

UK	626	Dr. Sandip Raha	Princess of Wales Hospital	Wales
UK	628	Dr. Nishthana Silva	Kings Mill hospital	Mansfield
Switzerland	501	Prof. Dr. med. Stephan Bohlhalter	Luzerner Kantonsspital Neurology and Neuroabilitation	Lucerne
Switzerland	502	Dr. Joan Michelis	Inselspital Universitätsklinik für Neurologie	Bern
Switzerland	503	PD. Dr. med. Georg Kägi	Kantonsspital St. Gallen Neurology Clinic	St.Gallen
Switzerland	504	Prof. Dr. med. Alain Kälin	Ospedale Civico, Neurocentro della Svizzera Italiana	Lugano
Switzerland	506	Dr Ettore Accolla	Kantonsspital Fribourg Service de neurologie	Fribourg

4. Other responsible parties

Project and site management, activation process, data banking, quality control and statistical analysis, were performed by Medineos, an IQVIA company based in Modena, hereafter called as MediNeos.

Study results were clinically reviewed and valued by the Study Outcome Review Board, composed of expert neurologists with long-standing experience in PD, namely:

- Prof. Giovanni Abbruzzese, DINOGMI - University of Genova, Italy
- Prof. Wolfgang Jost, Parkinson-Klinik Ortenau/University of Freiburg, Wolfach, Germany
- Prof. Jaime Kulisevsky, Sant Pau Hospital, Universidad Autonoma de Barcelona, Universitat Oberta de Catalunya, Ciberned, Spain

5. Milestones

Milestone	Planned date	Actual date	Comments
First EC Approval	June 2016	May 2016	
Last EC approval	January 2018	January 2018	
Start of data collection	June 2016	August 2016	
End of data collection	May 2019	June 2019	Target sample size reached on June 2018
Registration in the EU PAS register	March 2016	March 2016	EU PAS register number: EUPAS13745

Final report of study results	*October 2019*	*06/09/2019*	Final Statistical Report first version

6. Rationale and background

Parkinson's Disease (PD) is the second most common neurodegenerative disease following Alzheimer's disease. Approximately 1.2 million people live with PD throughout Europe and the number is expected to increase as the population is ageing. The incidence is approximately 1.5 times higher in males than females. The prevalence increases with age, from about 1.4% over the age of 60 to about 4.3% over the age of 85.[1]

PD occurs when, because of an unknown cause, dopamine-producing cells progressively degenerate.[1] This leads to progressive deterioration of motor function, progressive loss of muscle control and trembling. The impairment varies from individual to individual.

Not only neuromusculoskeletal and movement-related functions are involved by impairments, but also non-motor areas. In fact, a considerable reduction in quality of life is noticed. Examples of early non-motor impairments are depression, olfactory dysfunction, REM sleep behaviour disorder and constipation. In addition, mental impairments, specifically impaired executive function and memory, as well as prolonged reaction time can be present at diagnosis.[1]

The overall goal of PD management is to optimize activities, participation and quality of life of patients. Currently, the focus is on symptom control and compensation. Symptomatic treatments include a variety of drugs and rehabilitation. No treatment slows down disease progression.[1]

Current pharmacological management is largely based on the dopamine precursor L-dopa and dopamine agonists. L-dopa offers the best symptomatic relief of rigidity, bradykinesia and tremor. In addition to L-dopa, dopamine agonists are prescribed to alleviate other disabling complications such as restless legs syndrome, sleep fragmentation and early morning akinesia or dystonia.

L-dopa remains the most effective single therapy, but after years of administration it promotes often incapacitating motor fluctuations and might accelerate disease progression through free radical formation. Mono-Amine Oxidase (MAO)-B inhibitors improve motor function in PD patients when used as adjunctive therapy to L-dopa. Recently it has been suggested that they might also slow down disease progression by reducing oxidative damage.

Beyond dopamine, perturbations in neurotransmission in the basal ganglia of PD patients are known to involve glutamate and other transmitters, and these are believed to play important roles in the pathogenesis of primary symptoms, motor fluctuations, and possibly neuronal cell loss. Increasingly, non-dopaminergic agents are being studied to determine their potential to supplement, or delay the use of, established dopaminergic therapies.

Safinamide was developed as a new strategy for the therapy of PD, by combining inhibition of both MAO-B and sodium channels, leading to both dopaminergic and non-dopaminergic

activities.

Safinamide is an α-aminoamide indicated as add-on therapy for the treatment of patients with idiopathic PD, in mid-to late-stage fluctuating patients receiving a stable dose of L-dopa alone or in combination with other PD medications[10].

Efficacy and safety of safinamide were studied in a large number of clinical trials. In particular, the benefits of safinamide as add-on therapy to L-dopa and other dopaminergic treatments in mid-stage to late-stage PD patients with motor fluctuations were demonstrated in Study 016[11]. In this double-blind, placebo-controlled 24-week trial, 669 patients were equally randomized to receive 50 mg/day safinamide, 100 mg/day safinamide or placebo as add-on therapy to the stable L-dopa dose. Based on patient diaries, safinamide 50 mg/day and 100 mg/day increased total daily "on" time with no or non-troublesome dyskinesia.[10] Motor symptoms (Unified Parkinson's Disease Rating Scale (UPDRS) III), activities of daily living (UPDRS II), Clinical global impression (CGI)-S and quality of life (PDQ-39) also improved when compared with placebo. Concerning safety, overall, incidences of treatment emergent adverse events (TEAEs), drug-related TEAEs and discontinuation due to TEAEs with safinamide were similar to placebo.[10] This safety profile was similar to that observed in the 18-month extension study (Study 018), in which treatment with safinamide (50 and 100 mg/day) was generally well tolerated[12].

7. Research question and objectives

During the initial marketing authorization procedure, at day 180, the European Medicines Agency (EMA) recommended that the Applicant provide additional real world data on safinamide given the uncertainties regarding categories of patients not well represented in clinical trials, namely those aged > 75 and with concomitant psychiatric conditions such as psychosis, cognitive dysfunction and depression. Following this request, a Drug Utilization Study (DUS) aimed at investigating how safinamide is prescribed and used in routine clinical practice was designed. It allowed to evaluate not only the extent of these categories of patients, but also safety data (in terms of occurrence of adverse events). With this approach the opportunity of collecting and disseminating relevant data concerning the use of safinamide in a real-life setting was seized. In order to improve knowledge about the product beyond the findings of clinical trials, the study provided data on drug safety profile and on safinamide treatment patterns.

This observational study allowed obtaining information on safinamide safety and pattern of use in clinical practice during one year in the first post-commercialization phase of the product.

The aim of the study was merely descriptive and there were no pre-specified hypotheses.

Primary objective:

To describe the occurrence of adverse events in patients treated with safinamide in real-life conditions during one year in its first post-commercialization phase as reported by the Investigators.

The analysis was conducted overall and in some subgroups of interest, namely in patients aged >75 and those with relevant concomitant conditions.

Secondary objectives:

1. To describe the characteristics of patients treated with safinamide according to clinical practice (demographics, disease duration, disease severity, previous treatment for PD, concomitant relevant conditions with particular focus on psychiatric ones and related treatments).
2. To describe safinamide treatment patterns in a real-life setting (treatment duration, dose adjustments and interruptions, dose discontinuation and reason, changes in concomitant PD therapies, treatments for PD administered after safinamide).

8. Amendments and updates

During the notification process of this study to the German competent authority (BfArM), it was underlined by the competent authority that the study protocol did not suggest any off-label use of safinamide, but did not explicitly report that enrolment of off-label patients is forbidden in Germany either. Consequently, to be compliant to the German law AMG §4(23), BfArM asked to amend the study protocol for German sites involved in the SYNAPSES study.

According to BfArM request of 12 July 2016, the scope of the amendment of the study protocol was to avoid any inclusion of patients who could be treated not according to market authorization as described in the SmPC. The final modifications in terms of target population are reported in the "selection criteria" chapter.

9. Research methods

9.1. Study design

This was a multi-country multicentre retrospective-prospective cohort observational study.

The study lasted 34 months, including a 22-month enrollment period and 12-month follow-up period.

The cohort study was defined according to the primary objective of the study, that is the

description of the occurrence of adverse events in patients treated with safinamide in real-life conditions during one year in the first post-commercialization phase as reported by the Investigators.

Primary endpoints:

- Number of patients with adverse events (AEs), overall and by event description, not only considering all AEs but also for serious adverse events (SAEs) and adverse drug reactions (ADRs) related to safinamide, serious or not, separately.
- Description of some attributes of AEs, namely severity, seriousness, relation with safinamide according to clinician's judgment, action taken and outcome.
- Primary endpoints were also stratified by age (>75) and relevant concomitant conditions.

Furthermore, the following secondary endpoints were evaluated:

- Description of demographic and clinical baseline characteristics, including anamnesis of PD and previous treatments, or order to characterize the treated population.
- Description of safinamide treatment duration.
- Description of safinamide dose adjustments and interruptions, described by means of the proportion of patients experiencing at least one safinamide dose increase, dose decrease and dose interruption, respectively. If episodes of overdose were reported in the electronic case report form (eCRF), they were provided in the analyses.
- Description of safinamide discontinuation (proportion of patients experiencing such event) and reason.
- Description of changes in PD therapies concomitant to safinamide, intended as proportion of patients adding one or more active, stopping one or more active, changing dose of one or more active ingredient.
- Description of treatments for PD administered after safinamide.

All study endpoints were provided using descriptive statistics. In fact, the aim of the study was merely descriptive and there were no pre-specified hypotheses.

The study design allowed for a description of treatment patterns at enrolment and during the longitudinal observation. In most of the countries involved the study onset was expected to coincide with the drug commercialization. For this reason a prospective observation was chosen. Moreover, in order to include also patients starting treatment before the study onset, if any, a retrospective part of the observation period (expected to be experienced by a small number of patients) was allowed for.

9.2. Setting

The countries involved were Belgium, Germany, Italy, Spain, Switzerland and the United Kingdom. As safinamide was not reimbursed in France as per normal clinical practice, the study was not performed in this country.

The SYNAPSES study had foreseen an enrolment period (from August 4th, 2016 to June 12th, 2018), followed by an observational follow-up phase.

Data collection was performed between August 4th, 2016 (first patient first visit, FPFV) and June 17th, 2019 (last patient last visit, LPLV).

For countries in which the drug was commercialized after the FPFV date, the study started according to drug availability on the market and duration of the authorization phase.

About 140 neurology centres, specialist centres dealing with PD and geriatric centres, identified as those primarily involved in the administration of safinamide, were involved in the study and asked to consecutively enrol patients in the study, according to the inclusion/ exclusion criteria reported below. Finally, 136 sites confirmed their participation in the study and 128 enrolled a total of 1610 patients (vs 1600 expected to be included in the study).

.Due to the availability of the drug distribution and the site authorization process, the final number of patricipating sites and enrolled patients was not uniformly distributed among countries, but a uniform distribution among countries was not planned either. For this purpose, 42 sites were allowed to enrol more than 13 patients (Table 9.2.1).

Site	Total number of enrolled patients
ES402 - Hospital de Cruces	63
IT316 - Policlinico Tor Vergata	55
IT318 - Istituti Clinici di Perfezionamento	43
ES423 - Hospital de la Santa Creu i Sant Pau	38
IT310 - Ospedale San Raffaele Cassino	37
BE108 - AZ Sint-Jan	31
ES416 - Hospital Universitari Son Espases	30
DE215 - Uni-Klinik Münster, Klinik für Allgemeine Neurologie	29
ES422 - Hospital General Universitario de Elche	27
DE214 - Praxis für Psychiatrie und Neurologie Dr. Oehlwein	26
ES435 - Hospital Universitario Infanta Sofía	24
ES409 - Hospital Univeritario Puerta del Mar	23
IT334 - A.O.U. Policlinico-Vittorio Emanuele	23
IT344 - A.O.U. Policlinico P. Giaccone	22

Site	Total number of enrolled patients
ES441 - Hospital Santa Caterina	21
ES404 - Hospital Ramón y Cajal	20
IT315 - Ospedale San Giovanni Battista	20
DE201 - Gemeinschaftspraxis für Neurologie, Psychiatrie und Psychotherapie	19
IT301 - P.O. San Salvatore	18
BE104 - UCL Saint-Luc	17
BE109 - AZ Sint-Lucas	17
DE206 - Nervenärztliche Gemeinschaftspraxis	17
ES406 - Hospital Arquitecto Marcide	17
IT303 - A.O.U. Seconda Università di Napoli	17
IT320 - ASST Spedali Civili	17
BE110 - Jesse Ziekenhuis campus Virga Jessa	15
DE207 - Gesundheitszentrum Hoppegarten	15
ES408 - Hospital Universitari de Bellvitge	15
ES410 - Hospital Universitario La Princesa	15
ES438 - Hospital Central de Asturias	15
IT307 - Ospedale Bellaria	15
IT345 - Casa di Cura San Francesco	15
BE107 - CHU Tivoli	14
BE113 - CHU UCL Namur	14
DE205 - Praxis Prof. Dr. Kupsch, Ärztehaus BISMARCK KARREE	14
DE218 - Neurologische Praxis Siegen, Eugen Schlegel	14
ES415 - Hospital Quirón-Teknon	14
ES424 - Ruber Internacional	14
ES433 - Hospital Virgen del Rocío	14
ES436 - Hospital Universitario Infanta Leonor	14
IT314 - Policlinico Umberto I - Univ La Sapienza	14
IT326 - Istituto Neurologico Mediterraneo Neuromed	14
BE102 - CHU Sart Tilman	13
CH503 - Kantonspital St. Gallen, Klinik für Neurologie	13
DE216 - Parkinson-Klinik Ortenau GmbH & Co. KG, Zentrum für neurologische Bewegungsstörungen	13
GB625 - Fairfield General Hospital, Ward 19 Clinical Trials Unit	13
GB626 - Princess of Wales Hospital	13
GB628 - Kings Mill hospital	13
IT308 - Nuovo Ospedale Sant'Agostino-Estense	13

Site	Total number of enrolled patients
IT329 - Ospedale Generale Regionale F.Miulli	13
BE101 - UZA	12
BE111 - Algemeen Ziekenhuis Klina	12
BE112 - Clinique St. Pierre	12
DE211 - Kliniken Kreis Mühldorf am Inn, Parkinson und andere Bewegungsstörungen	12
ES403 - Hospital de Donostia	12
ES432 - Hospital Gregorio Marañon	12
IT311 - Università Cattolica S. Cuore Policlinico Gemelli	12
IT322 - Istituto Neurologico C. Mondino	12
BE106 - AZ Delta campus Wilgenstraat	11
ES407 - Hospital Virgen Macarena	11
ES412 - Xanit Hospital Internacional	11
ES420 - Hospital Público Universitario Del Henares	11
ES425 - Hospital Universitario de Burgos	11
GB610 - Greater Manchester Neuroscience Centre, Salford Royal NHS Foundation Trust	11
IT304 - A.O.U. OO.RR. S.Giovanni di Dio e Ruggi D'Aragona	11
IT306 - Arcispedale Sant'Anna	11
IT317 - Università degli Studi di Genova	11
IT319 - Ospedale San Raffaele	11
IT333 - A.O Riuniti Villa Sofia-Cervello	11
IT337 - A.O.U. Pisana Ospedale Santa Chiara	11
IT338 - Ospedale S. Maria della Misericordia	11
IT354 - Ospedale A.Perrino	11
CH502 - Universitätsklinik für Neurologie, Inselspital	10
DE210 - St. Josef-Krankenhaus Kupferdreh;; Neurologie	10
IT321 - ASST Santi Paolo e Carlo	10
IT325 - Fondazione Univ. D'Annunzio	10
IT330 - A.O.U. Policlinico Consorziale	10
IT348 - Ospedale di Cattinara	10
IT351 - Ospedale San Martino	10
CH504 - Ospedale Regionale di Lugano-Civico	9
DE221 - Neurologische Facharztpraxis, Dr. med. Ilias Nastos	9
ES413 - Hospital General Universitario de Ciudad Real	9
ES418 - Hospital Universitari i Politècnic La Fe	9
ES431 - Hospital Quirón	9

Site	Total number of enrolled patients
IT324 - A.O.U. Ospedali Riuniti	9
IT327 - A.S.O. Molinette	9
IT343 - Ospedale San Salvatore	9
IT349 - A.O.U. Maggiore della Carità	9
CH501 - Luzerner Kantonsspital, Zentrum für Neurologie und Neurorehabilitation	8
ES428 - Clínic Universitari Barcelona	8
ES430 - Clínica Universidad de Navarrra	8
IT313 - A.O. Sant' Andrea - Univ. La Sapienza	8
IT346 - Ospedale civile S.Maria delle Croci	8
CH506 - Hopital fribourgeois	7
ES426 - Hospital Virgen de la Salud	7
GB603 - Royal United Hospitals Bath NHS Foundation Trust	7
IT342 - Ospedale Civile Maggiore - Borgo Trento	7
IT347 - Ospedale S. Giovanni di Dio	7
DE217 - Praxis Dr. Blersch	6
ES401 - Hospital Puerta de Hierro	6
ES405 - Hospital Insular de Las Palmas	6
ES417 - Hospital General Universitario de Valencia	6
ES429 - Hospital Lozano Blesa	6
ES440 - Centro de Neurología Avanzada	6
GB614 - LIVEWELL Southwest	6
IT302 - IDC Capodimonte	6
IT309 - A.O.U. S.Maria della Misericordia	6
IT305 - Ospedale Maggiore	5
IT312 - Università Campus Bio-Medico	5
IT340 - Ospedale dell'Angelo	5
IT332 - A.O.U. Policlinico Monserrato	4
IT350 - Ospedale di Circolo e Fondazione Macchi	4
DE204 - Universitätsklinikum der Ruhr-Universität Bochum, Klinik für Neurologie	3
ES419 - Hospital General Universitario de Alicante	3
ES421 - Hospital de Tortosa Verge de la Cinta	3
IT331 - Azienda Ospedaliera G. Brotzu	3
IT335 - A.O.U. Policlinico G. Martino	3
IT339 - Ospedale San Camillo	3
IT352 - A.O. Santa Maria	3

Site	Total number of enrolled patients
BE103 - UZ Gent	2
BE105 - Hôpital Erasme	2
DE202 - Neurozentrum Stuttgart Mitte	2
ES437 - Hospital Universitario Lucus Augusti de Lugo	2
ES443 - Hospital Parc Sanitari Sant Joan	2
IT328 - Ospedale Cardinal Massaia	2
IT336 - Ospedale della Misericordia	2
ES414 - Hospital Universitari Vall d'Hebron	1
IT341 - Casa di Cura Villa Margherita	1

Table 9.2.1. Number of evaluable patients by site.

Country distribution of enrolled patients is reported in Figure 9.1, 70% of patients were included between Italy and Spain. Sites enrolling more than the double of the average (i.e. 26 patients or more) were in Spain (4 sites with respectively 63, 38, 30 and 27 patients each), Italy (3 sites with respectively 55, 43 and 37 patients each), Belgium (1 site with 31 patients) and Germany (2 sites with 29 and 26 patients each).

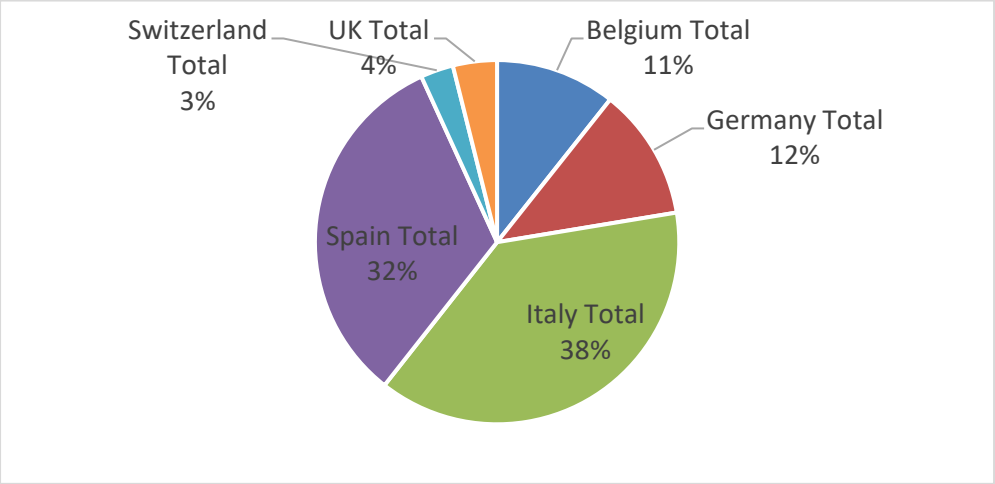


Figure 9.1 Country Distribution of enrolled patients.

9.3. Subjects

Adult patients treated with safinamide according to clinical practice were consecutively enrolled in each participating site during the 22-month recruitment period.

Inclusion criteria (at enrolment visit):

- Adult male and female patients (≥18 years).

- Patients who start treatment with safinamide at enrolment visit or who started it in the previous four months, according to clinical practice after its commercialization. This is an observational study, hence the physician's decision of starting treatment with safinamide has been taken before the patient's inclusion in the study and is completely independent from the study protocol.
- Patients who have signed informed and privacy form consent according to local legal requirement.
- *Germany only:* Patients with confirmed diagnosis of idiopathic Parkinson's disease who present administration of safinamide in accordance with the local SmPC

Exclusion criteria (at enrolment visit):

- Patients participating in any clinical trial on safinamide at study inclusion.
- *Germany only:* patients presenting contraindications to safinamide listed in the local SmPC.

In order to ideally observe the largest population of patients administered with safinamide according to the clinician's decision in its first post-commercialization phase, this study avoided any selection of patients by means of broad inclusion/exclusion criteria. As for inclusion criteria, adult patients giving their consent to participate in the study were eligible if they start treatment at the enrolment visit or in the previous four months according to clinical practice. This limit was set in order to allow no more than one time point (start of treatment) for which data are retrospectively collected, leading to the exclusion of a reasonably negligible number of patients given the time elapsed from drug commercialization. With the exception of Germany, PD was not defined as an inclusion criterion in order to have the possibility of observing patients with a different diagnosis than PD if they are administered safinamide. This allowed for a more complete picture of drug utilization in a real-life setting.

With the exception of Germany, the only exclusion criterion consists in patients receiving safinamide in a clinical trial, according to the observational nature of the study.

Exit criteria (at any time during the study):

- Informed consent withdrawn
- Loss to follow-up
- Patients included in any clinical trial on safinamide
- Pregnancy
- Death

Patients were included in the study when they started treatment with safinamide or if they started this treatment in the following four months. This was an observational study, hence the physician's decision of starting treatment with safinamide was taken before the patient's inclusion in the study and was completely independent from the study protocol. All patients were followed for 12 months after the start of treatment. If a patient discontinued treatment with safinamide during the study, the observation continued. Data were collected at treatment start, and during study visits after 4 , 8 and 12 months . One-month tolerance was provided for each study visit by study protocol, in order to maximize the uniformity of observations among patients. However patients performed follow-up visits according to routine practice. If the patient was enrolled at the start of treatment, then all data were prospectively collected. Otherwise, if the patient was enrolled after the start of treatment, then the data collection was partially retrospective.

The study scheme is shown in Figure 9.3.1.

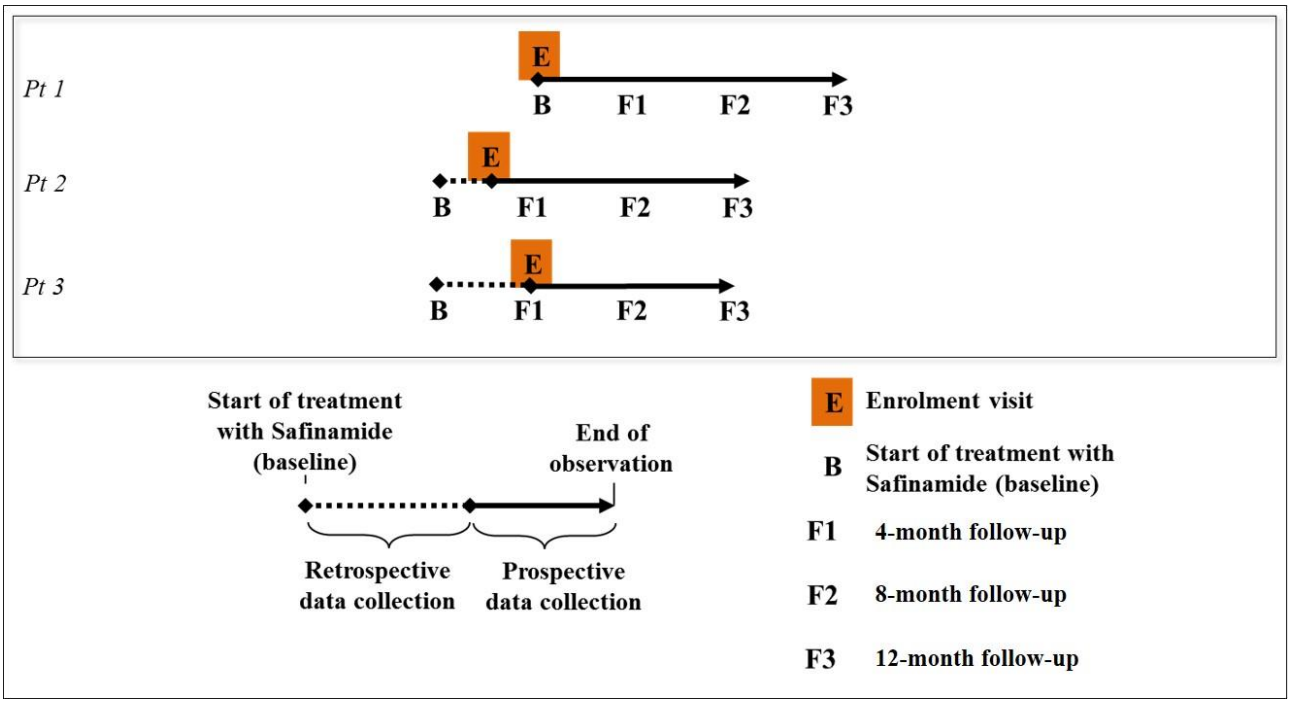


Figure 9.3.1. Study scheme.

Pt 1. Patient enrolled at the start of treatment with safinamide. The enrolment visit was performed at treatment start and then the patient was prospectively followed for 12 months, performing 4-, 8- and 12-month follow-up visits.
Pt 2. Patient enrolled two months after the start of treatment with safinamide. Data at the start of treatment were retrospectively collected at enrolment visit, as well as data regarding the two months passed, while the patient was prospectively followed until 12 months after the start of treatment, performing 4-, 8- and 12-month follow-up visits.
Pt 3. Patient enrolled four months after the start of treatment with safinamide. Data at the start of treatment and at four months after were collected at enrolment visit, as well as data regarding the four months passed, while the patient was prospectively followed until 12 months after the start of treatment, performing 8- and 12-month follow-up visits.

9.4. Variables

Exposure

The exposure of interest was the treatment with safinamide, administered to all eligible patients as per clinical practice. All patients receiving at least one dose of safinamide were considered as exposed. Treatment with safinamide was recorded since its start: in fact patients were enrolled either when they start safinamide or up to four months after safinamide start. Data on safinamide treatment were recoded according to clinical practice and updated in continuum during the course of the study.

Investigated outcomes

- Number of patients with AEs, intended as the proportion of patients experiencing at least one AE from the start of treatment with safinamide until the end of the observation period, overall, by System Organ Class (SOC) and by Preferred Term (PT), according to the Medical Dictionary for Regulatory Activities (MedDRA).
- Number of patients with SAEs (adapting the definition of number of patients with AEs accordingly), overall, by SOC and by PT, according to MedDRA.
- Number of patients with ADRs related to safinamide (adapting the definition of number of patients with AEs accordingly), overall, by SOC and by PT, according to MedDRA.
- Description of AEs occurred in terms of severity, seriousness, relation with safinamide according to clinician's judgment, action taken and outcome.
- Demographics (gender, age, race).
- Disease duration at the start of treatment with safinamide, computed as the difference between the year of treatment start and the year of first diagnosis of PD.
- Disease severity (Hoehn & Yahr stage).
- Concomitant relevant conditions, with particular focus on psychiatric ones and related treatments.
- Previous treatment for PD (in the past three months).
- Safinamide treatment duration, computed as the difference between:
    - The end of treatment and the date of treatment start for patient discontinuing safinamide during the study
    - The 12-month follow-up visit/ study withdrawal and the date of treatment start for patient not discontinuing safinamide during the study

- Safinamide dose adjustments, interruptions, discontinuation and reason for discontinuation.
- Changes in PD therapies concomitant to safinamide and treatments for PD administered after safinamide.
- Motor Evaluation (only PD patients), as measured by UPDRS III (see 9.4 Data sources for details)

Details of collected variables are reported in Table 9.4.1.

This was an observational study, it did not interfere with, or impose any therapy protocols, diagnostic/ therapeutic procedures or visit schedules. Patients were treated according to local prescribing information and clinical judgment, and assessments performed according to site clinical practice.

Investigators were asked to report the requested data in the eCRF. All data were reported by the clinician.

The following variables were expected to be collected with respect to each time point, as per clinical practice. If data were not available, the Investigator reported "NA".

	Start of treatment with safinamide [a]	**4 (±1) months after start of treatment**	**8 (±1) months after start of treatment**	**12 (±1) months after start of treatment**	**Study completion**
Inclusion/ exclusion criteria, informed consent and privacy signature (evaluated at enrolment)	X *				
Socio-demographics (gender, age, race)	X				
Medical history: concomitant relevant conditions with particular focus on psychiatric ones and related treatments	X	X	X	X	
Anamnesis of PD or Parkinsonism (year of first diagnosis, year of first symptom onset, motor and non-motor symptoms, Hoehn & Yahr stage, caregiver y/n)[b]	X			X[e]	
Previous treatments for PD or Parkinsonism – last three months (active, dose, start, end date) [b]	X				

Treatment with safinamide (start date, initial daily dose and number of tablets, dose changes and interruptions, dose discontinuation with reason, end date/ ongoing at study completion)		*continuum*			
Concomitant treatments for PD or Parkinsonism and related conditions (active, start date, initial dose, dose changes/ interruptions/ discontinuation, end date/ ongoing at study completion) [b]	X	X	X	X	
Concomitant treatments for any other medical condition			*continuum*		
Treatments for PD or Parkinsonism subsequent to safinamide (active, dose, start date, end date/ ongoing at study completion) [b]		X	X	X	
Adverse Events (AEs)			*continuum*		
Occurrence of other safety special events y/n		X	X	X	
Pregnancy y/n			*continuum*		
Unified Parkinson's Disease Rating Scale (UPDRS) [c]	X[d]	X[d]	X[d]	X[d]	
Change in fluctuating/no fluctuating and type of fluctuation [c]	X	X	X	X	
Last available cognitive evaluation, if any	X				
Observation completed y/n, if no date and reason of withdrawal					X

Table 9.4.1. Collected variables.
[*] in the case of retrospective observation, inclusion/ exclusion criteria were evaluated and informed consent and privacy signature were obtained at enrolment visit.
[a] If the patient started treatment with safinamide before the inclusion visit, these data were retrospectively collected at enrolment visit.
[b] In the case of patients with diagnosis other than PD or other Parkinsonisms which are not related to PD, the collection of these data was adapted.
[c] Only for PD patients.
[d] The questionnaires were administered during the prospective observation period (i.e., excluding the retrospective period).
[e] Only Hoehn & Yahr stage

The study was not aimed at evaluating any associations but investigated outcomes were described. Thus, there were no confounders or effect modifiers which could have altered associations. Nevertheless, patient and treatment characteristics were collected and taken into

consideration for the interpretation of results.

9.5. Data sources and measurement

The physicians and their staff were trained before study initiation.

Given the observational nature of the study all activities concerning patient management, including medical charts updating and maintenance, were conducted in compliance with the clinical practice of the participating centres.

For all patients enrolled in the study after the signature of the Informed Consent, data were prospectively recorded on the Study eCRF by the Investigator both by retrieving already available data from the medical charts and by interviewing the patient in order to collect information that, as per single centre practice, would not have been reported in the patient's medical chart.

The Investigator was asked to record all AEs (serious or otherwise, related or not to safinamide) and pregnancy cases which occurred during the observation period and of which he/she becomes aware.

For patients starting treatment with safinamide (Xadago®) before the enrolment visit, data on treatments and on safety outcomes were collected retrospectively from each patient's medical charts at the moment of the enrolment in the study; they were later integrated/updated with information routinely available in the patient's medical charts and with those specifically collected interviewing the patient at each subsequent study visit.

During the visit, in the case of patients who were capable of giving an answer but not able to read or write, a third person (e.g. site staff or caregiver) could report answers after asking questions to the patient himself and according to his indications.

PD patients were evaluated with the **Unified Parkinson's Disease Rating Scale (UPDRS).** UPDRS was originally developed in the 1980s[13] and became the most widely used clinical rating scale for PD[14] in order to follow in a more objective manner the progression of symptoms in patients treated with a specific drug. It consists of 55 items and it is divided in four parts. If all of them are administered, then a sum score for each part is obtained. The UPDRS is filled in by the clinician upon the observation and interview to the patient. Only an English version is available worldwide and - as the instrument was filled in by the investigators - the questionnaire was administered in English language to all the participating sites.

9.6. Bias

The number of patients with a partially retrospective observation period was expected to be small. However, in order to evaluate the potential impact of recall bias on the primary endpoint, the proportion of patients experiencing any AE excluding those who started treatment with safinamide before study inclusion was provided as sensitivity analysis.

This observational study allowed for obtaining information on safinamide safety and pattern of use in clinical practice during one year in the first post-commercialization phase of the product. Included patients constitute a convenience sample of all those who were administered safinamide during the study period because no random procedure was applied in site and patient selection. Consecutive enrolment was requested by the protocol, in order to minimize any selection bias.

9.7. Study size

The primary objective of the study was to describe the occurrence of adverse events in patients treated with safinamide in real-life conditions during one year in its first post-commercialization phase as reported by the Investigators.

A total of 1600 patients were expected to be enrolled in the study. This sample size was defined based on feasibility considerations concerning the length of the enrolment period and site capacity. Considerations on the achievable precision of the estimates are presented below.

No results from studies investigating safinamide in a real-life setting were available, therefore safety data were only available from clinical trials. Study 016 was a double-blind, placebo-controlled, parallel-group, randomized, multi-centre, multi-national, phase III trial, comparing two fixed doses of safinamide (50 and 100 mg/day, p.o.) versus placebo as add-on therapy to an optimized dose of L-dopa along with other PD drugs.[10] Out of 447 patients treated with safinamide for 24 weeks, 65.8% experienced TEAEs. More specifically, for example, 14.1% of safinamide patients experienced musculoskeletal and connective tissue disorders and 4.9% back pain.

Based on 1600 enrolled patients, 20% as drop-out rate (leading to 1280 evaluable patients) and on the expected proportions described above, the 95% confidence interval (CI) of the expected proportion was evaluated, as shown in Table 9.7.1.

	N. of evaluable patients	**Expected proportion**	**Two-sided 95%CI of the expected proportion**
% patients with any TEAE	1280	65.8%	(63.2% ; 68.4%)

% patients with any musculoskeletal and connective tissue disorder	1280	14.1%	(12.2% ; 16.0%)
% patients with back pain	1280	4.9%	(3.7% ; 6.1%)

Table 9.7.1. Two-sided 95% confidence interval of the expected proportion of patients with listed events, assuming 1280 evaluable patients.[24]

A sample size of 1280 evaluable patients allowed for observing expected rates equal to or higher than 3.3% with ≤ 30% relative error (computed as the ratio between the 95% CI half-width and the expected rate).

Furthermore, it was of interest to examine safety variables in subgroups of interest, namely patients aged >75 and those with relevant comorbidities, with a particular focus on psychiatric conditions. The proportion of patients aged >75 was expected to be about 25% according to clinicians' opinion and to demographic characteristics of PD patients in most of the literature.

In the double-blind, placebo-controlled studies in late stage PD patients (Studies 016/018 and 27919 (SETTLE)) (data not published at the time of protocol writing), in which patients could be treated for up to two years, a total of 27 patients aged >75 were randomized to safinamide, while 20 patients in this age range received placebo. Out of 27 safinamide patients, 25 (92.6%) experienced TEAEs. More specifically, for example, four (14.8%) experienced respiratory, thoracic and mediastinal disorders.

Table 9.7.2 shows a 95% CI of the expected rate in the subgroup of patients aged >75, based on 1600 enrolled patients, 25% aged >75 and 20% as drop-out rate (i.e. 320 evaluable patients).

	N. of evaluable patients	**Expected rate**	**Two-sided 95%CI of the expected rate**
% patients with TEAE	320	92.6%	(89.7% ; 95.5%)
% patients with any respiratory, thoracic and mediastinal disorder	320	14.8%	(10.9% ; 18.7%)

Table 9.7.2. Two-sided 95% confidence interval of the expected rate of patients with listed events, based on 320 evaluable patients aged >75.

With a sample size of 320, a two-sided 95% confidence interval for a single rate using the large sample normal approximation extends the 3.9% from the observed rate to an expected rate of 14.8%.[24]

In the case of a sample size < 1600 patients due to lower-than-expected actual accrual rate or duration of enrolment period in some countries or sites, a worst estimate precision would have been obtained. Considering 14.8% as the expected rate of patients with any respiratory, thoracic and mediastinal disorder in the subgroup of patients aged >75, then the number of evaluable patients leading to a relative error of the estimate lower than 30% would be 246, corresponding to 307 enrolled patients. Assuming that patients aged >75 constitute 25% of the whole sample, this means 1228 enrolled patients.

9.8. Data transformation

An eCRF was filled in by the Investigator and/or his/her designee.

All patients who signed the informed and privacy form consent were databased.

Each participating site maintained appropriate medical and research records for this study, in compliance with GPP, regulatory and institutional requirements for the protection of confidentiality of patients.

Patient initials or names were not recorded in the database: patients were associated with a unique identifier.

The eCRF used for the study was validated according to GAMP5. The IT infrastructure supporting the eCRF solution was monitored and controlled both in terms of Security (i.e. Intrusion Detection, Antiviruses, etc …) and Operational Performance. Backups and operative checks were properly managed in order to guarantee business continuity.

Front-end edit checks were run at the time of data collection and back-end edit checks were used by the Data Manager to prevent any discrepancies and to ensure consistency and completeness of the data.

Adverse Event terms (AEs, SAEs, and ADRs) were coded with the MedDRA dictionary version 21.1. Coding was performed at the end of the study and periodically during data collection. If some Adverse events were typed in a language different form the one used for encoding (English), they were translated and then encoded. Coding was performed at the SOC and PT level, and when ambiguos information was reported the term to be used was selected by the clinical data manager in agreement with the Sponsor. In case of dubious information, the Sponsor's medical judgement was used to select the proper term. Correspondence between coded term and original values were shared with the Sponsor.

Adverse events were reconciled at the end of data collection with the Sponsor's safety database (100% of events were reconciled). All discrepancies were evaluated and solved or considered acceptable.

Once the database was declared complete and accurate, it was locked and used for statistical analysis. Statistical tests were performed using the SAS software.

Due to the observational nature of the study no independent review of the data was performed.

The main computed variables (and algorithm of computation) are reported below.

Concomitant treatment with other monoamine oxidase (MAO) inhibitors during the observation period.
To evaluate if a MAO-inhibitor treatment was concomitant to safinamide, the following algorithm was performed:
At least one row having Trade name (coded according to WHO dictionary) in ATC classes: N06AF (Monoamine oxidase inhibitors, non-selective), N04BD (Monoamine oxidase B inhibitors), N04AG (Monoamine oxidase A inhibitors) with overlapping of at least one day between safinamide treatment and MAO inhibitors.
In the case of a missing day in theParkinsonism treatment Start/Stop date, the first day of the month was considered. In the case of missing day and month, 1st and July were considered, respectively.

Time from PD diagnosis: time occurred from PD diagnosis was calculated as the difference between the start year of safinamide treatment and the year of the first PD diagnosis.
Time from PD diagnosis (years) was considered 0 when Year of diagnosis was the same as Year of safinamide treatment start.

Time from PD onset of symptoms: time occurred from PD onset of symptoms was calculated as the difference between the start year of safinamide treatment and the year of first symptom onset. It was considered 0 when Year of PD onset of symptoms was the same as Year of safinamide treatment start.

Age at onset of symptoms: age at onset of symptoms was calculated as the difference between age at enrolment (years) and the difference between the year of start of safinamide treatment and and the year of onset of symptoms.

Observation period end date
The observation period end date was computed as follows:

- If the patient completed the study, then the observation period end date was equal to the 12-month Follow-up visit date.
- If the patient did not complete the study, then the observation period end date was equal to the date of premature withdrawal.

In the case of missing Study completion form or 12-month Follow-up, the observation period end date was computed as the maximum between the follow-up visit date at 4, 8 months follow-up and the date of safinamide treatment discontinuation (when applicable).

UPDRS (Unified Parkinson's Disease Rating Scale)
UPDRS consists of 55 items and it is divided in four parts. If all of them were administered, then a sum score for each part is obtained[5].

Evaluability for the scale:
Patients were evaluated independently for each UPDRS part and for the total score. All subjects that filled in all items of a specific part were considered evaluable for that UPDRS part. This was applied for part I, II, III and IV. As regards the total score, patients who have available scores for parts I, II,III and IV were considered for the total score too.
Scales which were missing for all items were not been considered evaluable.
Score calculation
Part I: sum of items from 1 to 4. Score range: 0-16
Part II: sum of items from 5 to 17. Score range: 0-52
Part III: sum of items 18, 19, 20 Face lips chin, 20 Right Hand, 20 Left Hand, 20 Right feet,

20 Left feet, 21 right, 21 left, 22 neck, 22 right Upper Extremity, 22 left Upper Limb, 22 right Lower Limb, 22 left Lower Limb, 23 right, 23 left, 24 right, 24 left, 25 right, 25 left, 26 right, 26 left, 27, 28, 29, 30, 31. Score range: 0-108

Part IV: sum of items from 32 to 42. Score range: 0-23.

UPDRS Total Score (range 0-199): sum of subscales I, II, III, IV scores

Missing data handling: not applicable.

The difference between UPDRS score (total and motor evaluation (Part III)) at follow up (4-8-12 month) and at baseline was computed.

Safinamide temporary interruption

Safinamide temporary interruption occured if at least one record of the TREATMENT WITH SAFINAMIDE log form had the field "Stop date with respect to this dose (dd/mmm/yyyy)" filled in, and was followed by another record of the TREATMENT WITH SAFINAMIDE log form (chronologically succeeding the first one) having safinamide start date > than the previous safinamide stop date + 2 days.

Safinamide permanent discontinuation

Safinamide permanent discontinuation occurred if:

- The question "Was the treatment with safinamide permanently discontinued after this dose?" was = "Yes" and
- Safinamide date of permanent discontinuation was ≤ of the observation period end date.

Initial administered safinamide daily dose

The log form of the treatment with safinamide was ordered by ascending date.

SAFINAMIDE start date: the first record was considered as initial administered safinamide.

Safinamide initial administered daily dose was described according to the following three categories:

- one 50 mg tablet per day
- two 50 mg tablets per day
- one 100 mg tablet per day
- Other: specification of number of tablets and daily dose administered.

Safinamide daily dose change during observation period

Safinamide daily dose change was computed as the first occurrence of "Was this daily dose changed?" = "Yes" and "If yes, specify" = not missing, having start date of the changed dosage before observation period end date.

Safinamide non-appropriate use at the start of treatment

Non-appropriate use was considered in the following cases:

1. Patients with Parkinson's disease different from Idiopatic PD
2. Patients without levodopa in addition to safinamide: No rows having Trade name (coded according to WHO dictionary) = "Levodopa" or at least one row having Trade name (coded according to WHO dictionary) = "Levodopa" with start date > Start date of safinamide or Levodopa stop date < Start date of safinamide
3. Patients without fluctuation at the start of treatment with safinamide
4. Patients who started safinamide with a dosage different from 50 mg/die
5. Patients with severe hepatic impairment
6. Patients with albinism, retinal degeneration, uveitis, inherited retinopathy or severe progressive diabetic retinopathy

7. Patients treated with Pethidine.
   At least one row with Trade name (coded according to WHO dictionary) = PETHIDINE HYDROCHLORIDE, PETHIDINE with:
   - *Petidine start date ≤ Start date of safinamide* and
   - *Petidine stop date missing or > Start date of safinamide*

8. Patients in concomitant treatment with other monoamine oxidase (MAO) inhibitors.
   At least one row having Trade name (coded according to WHO dictionary) in ATC classes: N06AF (Monoamine oxidase inhibitors, non-selective), N04BD (Monoamine oxidase B inhibitors), N04AG (Monoamine oxidase A inhibitors) with:
   - *MAO start date ≤ Start date of safinamide and*
   - *MAO stop date missing or MAO stop date >=Start date of safinamide*

Previous and terminated treatments for Parkinson disease
All treatments having:.
- Variable "Trade name" not missing AND
- Start date missing or < Start date of safinamide (dd/mmm/yyyy)) AND
- Variable "Date of permanent discontinuation dd/mmm/yyyy" not missing AND
- "Date of permanent discontinuation dd/mmm/yyyy" < Start date of safinamide (dd/mmm/yyyy)

Treatments trade names were grouped and described according to the following categories:
- Levodopa
- Dopamine agonists
- MAO-B inhibitors
- COMT inhibitors
- Anticolinergics
- Amantadine
- Others

In the case of a missing day of Parkinsonism treatment Start/ Stop date, the first day of the month was considered. In the case of missing day and month, 1st and July were considered, respectively.

Treatments for Parkinson disease ongoing at the start of safinamide treatment
All treatments having stop date (dd/mmm/yyyy) missing or ≥ start date of treatment with safinamide (dd/mmm/yyyy) AND having start date missing or ≤ Start date of safinamide (dd/mmm/yyyy))
Treatments trade names were grouped and described according to the following categories:
- Levodopa
- Dopamine agonists
- MAO inhibitors
- COMT inhibitors
- Anticolinergics
- Amantadine
- Others

Other treatments do not include psychiatric therapies

Only for MAO inhibitors
All treatments having stop date (dd/mmm/yyyy) missing or > start date of treatment with safinamide (dd/mmm/yyyy) AND having start date missing or <= Start date of safinamide (dd/mmm/yyyy))
In case of missing day of Parkinsonism treatment Start/ Stop date the first day of the month was considered. In case of missing day and month 1st and July were considered, respectively.

Psychiatric therapies ongoing at the start of safinamide treatment
Psychiatric therapies were evaluated singularly (i.e. not as combinations) and were classified as:

- antidepressants
  - tricyclic
  - SSRI
  - SNRI
- antipsychotics
- procholinergics (anticholinergics)
- Others

Furthermore, at each visit, treatments were defined as corresponding to the specific visit if they were ongoing, namely if they had Date of permanent discontinuation not missing and > date of visit OR Date of permanent discontinuation missing.
In the case of a missing day of psychiatric therapy Start/ Stop date, the first day of the month was considered. In the case of a missing day and month, 1st and July were considered, respectively.

Treatments for any other medical condition received during observation
All treatments having

- start date missing or < observation period end date (as defined above) AND
- end date (dd/mmm/yyyy) = missing or end date (dd/mmm/yyyy) > start date of treatment with safinamide (dd/mmm/yyyy).

Treatment trade names were coded as actives.

A patient could receive more than one treatment for any other concomitant condition.

In the case of a missing day of Treatment for any other medical condition Start/ Stop date, the first day of the month was considered. In the case of missing day and month, 1st and July were considered, respectively.

Adverse Events during observation
All events having onset date >= Start date of safinamide treatment (dd/mm/yyyy) and onset date ≤ Observation period end date (as defined above)
In the case of a missing day of Adverse Event onset date, the first day of the month was considered. In the case of missing day and month, 1st and July were considered, respectively. An exception was made for:

- *Adverse Event onset date with day NK, same year/month of safinamide start date: the adverse event was considered*
- *Adverse Event onset date with day/month NK, same year of safinamide start date: the adverse event was considered*

If Adverse Event onset date is completely Not Known or Observation period end date is missing, *the adverse event was considered.*

Furthermore, Adverse events were reconciled at the end of data collection with Sponsor's safety database (100% of events were reconciled). All discrepancies were evaluated and solved or considered acceptable.
Some adverse events (having associated more than one preferred term) were separated during data analysis.

ADR
For data analysis, Adverse Drug Reaction (ADR) was defined as an Adverse Event having a causal relationship to safinamide other than Not Related.

As per protocol, during data collection, adverse events were considered reportable for expedited safety reporting as Individual Case Safety Report (ICSR) when causality to safinamide was recorded as definite, probable, possible, unlikely and unclassifiable.

SADR
For data analysis, Serious Adverse Drug Reaction (SADR) was defined as a Serious Adverse Event having a causal relationship to safinamide other than Not Related

As per protocol, during data collection, adverse events were considered reportable for expedited safety reporting as Individual Case Safety Report (ICSR) when causality to safinamide was recorded as definite, probable, possible, unlikely and unclassifiable.

Incidence Rate (monthly)
IR was calculated as the ratio between the number of events and the sum of person-time in months.

Person time in months was calculated as (*Observation period end date – Start of treatment with safinamide)/30.4375.*

For two patients with observation period end date missing, the Person time in months was calculated as (AE Onset date – Start of treatment with safinamide)/30.4375.

Patients with special safety situations during observation
Patients with at least one special safety situation associated with the use of safinamide (Did a special safety situation associated to the use of safinamide occur?) ≠ none) and at least one record not missing.

Moreover, the following criteria were applied for definition of subgroups of patients:

- ***Patients aged > 75:*** *Age at enrolment visit (years) > 75*
- ***Patients with relevant comorbidities****: patients presenting any other clinically medical condition ongoing at the start of treatment with safinamide= Yes.*
- ***Patients suffering from psychiatric conditions:*** *patients presenting any psychiatric condition ongoing at the start of treatment with safinamide = Yes or Does the patient receive any treatment for psychiatric conditions at the start of treatment with safinamide?= Yes*

9.9. Statistical methods

9.9.1. Main summary measures

Data were described on all enrolled patients fulfilling inclusion/exclusion criteria.

The statistical analysis were done on all "evaluable patients for the Full Analysis Set" defined as the patients satisfying all inclusion criteria, not violating any exclusion criteria enrolled in the allowed enrolment period (01/08/2016-01/06/2018). Ten minor violations were accepted as evaluable patients because patients had received information on the study during recruitment period, but signed the informed consent form after the end..

Moreover, for analysis of follow up data only patients evaluable at 4-, 8- or 12-month follow up were considered; they were defined as the patients evaluable for the Full Analysis Set with data collected at 4+/- 1.5 month, 8 (+/-2) month and 12 (+/-2) month after the start of treatment with safinamide. These ranges took into account the routine practice setting and they were discussed during the Data Review Meeting and specified in the Statistical Analysis Plan final version approved before DB lock.

The aim of the study was merely descriptive and there were no pre-specified hypotheses.

Categorical variables were described by means of absolute and relative frequencies, while continuous variables by means of mean, standard deviation, quartiles, min and max.

9.9.2. Main statistical methods

The primary objective of the study was to describe the occurrence of adverse events in patients treated with safinamide in real-life conditions during one year in its first post-commercialization phase as reported by the Investigators. The number of patients with AEs (portion of patients experiencing at least one AE from the start of treatment with safinamide until the end of the observation period), overall and by SOC and PT according to MedDRA were provided. The number of patients with SAEs, and ADRs related to safinamide, serious or not, were provided as well.

The analyses were provided overall and for subgroups of interest: patients aged >75 and those with relevant comorbidities other than those concomitantly suffering from psychiatric conditions.

Specifically, data were provided in the group of patients suffering from psychiatric conditions (i.e. psychosis, bipolar disorder and severe depression, etc).

Furthermore seriousness, severity, relation with safinamide according to Investigator judgment, action taken and outcome of the event were summarized.

As for secondary objectives, the following analyses were provided.

1. <u>To describe the characteristics of patients treated with safinamide according to clinical practice</u>

   Enrolled patients were described with respect to demographics, namely gender, age and race, and clinical variables, namely diagnosis, disease duration and severity. Previous treatment for PD (last year) was summarized. Concomitant relevant conditions, with a

particular focus on psychiatric ones, and related treatments were described.

2. For patients having a diagnosis other than and not related to PD, the details of diagnosis and relevant previous (last year) treatments was provided. This case did not occur in the data. To describe safinamide treatment patterns in a real-life setting:
    - Safinamide treatment duration was reported, including the number of patients still receiving safinamide at the end of observation.
    - The initial administered daily dose and the initial number of daily tablets was reported.
    - The proportion of patients with dose increase and dose decrease was provided, as well as those of patients temporary interrupting treatment.
    - The number of episodes of overdose was reported, if any.
    - The percentage of patients discontinuing safinamide was described and the reasons were summarized.
    - Treatments for PD still ongoing at the start of treatment with safinamide and changes in concomitant therapies during the treatment period were described.
    - Finally, treatments for PD administered after safinamide were provided as well.

Moreover, as additional objectives evaluated on PD patients, the analysis of UPDRS scores was summarized at each time point.

Data collected on all patients were considered as pooled for statistical analyses. Stratifications by country were not foreseen because there were no reasons for which differences among countries were expected and they were not of interest for this study anyway. Study objectives were evaluated overall on the sample of first patients treated with safinamide in clinical practice.

Study results were clinically reviewed and valued by the Study Outcome Review Board, composed of expert neurologists with long-standing experience in PD, namely:

- Prof. Giovanni Abbruzzese
- Prof. Wolfgang Jost
- Prof. Jaime Kulisevsky

SAS for Windows Version 9.4 and SAS Enterprise Guide 7.1 were used for statistical analyses.

9.9.3. Missing values

Patients with missing values were not excluded from the analysis, but their data were not replaced; frequency of missing data was given for all analyzed variables.

9.9.4. Sensitivity analyses

The number of patients with a partially retrospective observation period was expected to be small. However, in order to evaluate the potential impact of recall bias on the primary endpoint, the proportion of patients experiencing any AE, excluding those who started treatment with safinamide before study inclusion, was provided as sensitivity analysis.

9.9.5. Amendments to the statistical analysis plan

Not applicable. However after the delivery of the final statistical report first version, the definition of ADR and SADR was modified in order to make it consistent with periodic PV reporting; specifically, the statistical analysis plan reported ADRs (SADRs) which were all (serious) AEs with probable or possible or definite causality, whereas during reporting unclassifiable and unlikely events were considered too. This latter definition was finally used in the Final version of the statistical report (attached).

9.10. Quality control

The Quality control was managed in accordance with Medineos procedures as agreed with Zambon.

Actions to improve the quality of data were taken in different moments during the study and using various tools concerning monitoring, data cleaning and statistical analysis. A risk-based approach was followed during the whole study: for each phase, critical variables and activities were identified and put under control.

Each enrolling site received at least one on-site monitoring visit according to the Source Data Verification (SDV) plan as reported below:

- 100% of Inclusion/exclusion criteria
- 100% of Informed consent forms and documentation of subject participation on Source Data
- 100% of SAEs and ADRs related to safinamide
- 100% of pregnancies

For the first and last subject, and every fifth enrolled subject (5, 10, 15, 20, etc.):

- Check source data for special situations: overdose, abuse, off-label use, misuse, medication error, occupational exposure and use during breastfeeding, as well as cases of suspected drug interaction and lack of efficacy associated to an ADR
- Demographic and clinical baseline characteristics, including anamnesis of PD and previous treatments, or order to characterize the treated population.
- Safinamide treatment information (i.e. prescription according to approved indication, start date, start dose, dose increase, dose decrease and dose interruption).
- PD therapies concomitant to safinamide and, if applicable, PD treatments after safinamide discontinuation.

According to the number of patients enrolled, the number of on-site monitoring visits was adjusted for each site in order to allow to follow the SDV plan reported above.

Data validation covered both on-line (electronic CRF allowed to verify data when they were entered by means of automated edit checks, out of range controls, etc.) and off-line checks. Subsequently, quality control continued at the moment of the database lock when the Clinical Data Manager (CDM) locked the database upon the Biostatistician's (BS) review of the obtained quality of data, and evaluation of the impact of possible missing/inconsistent data after the data cleaning process.

Finally, a quality control on the data analysis process focused on the detection of possible calculation errors or inconsistent data was performed. The following quality controls were performed on the statistical report of the SYNAPSES study:

- All the tables described in this document were programmed and verified by a BS.
- An independent oversight of the final statistical report was performed as conceptual review of results, in order to evaluate their coherence and plausibility.
- All the tables in this report were independently reviewed to verify their consistency.

Moreover, the following tables were reprogrammed or independently verified by another BS or CDM, as detailed for each point:

- Enrolled and evaluable patients. CDM verified 100% of computed variables for evaluability criteria (baseline an follow-up) with respect to the algorithms described in the SAP. Another BS or CDM verified the table independently with respect to raw output.
- Evaluable patients by population subgroups. Another BS/CDM verified 100% of computed variables.
- Patient status at the start of treatment with safinamide by patient age. Another BS/CDM verified 20% of computed variables for motor symptoms and non-motor symptoms.
- UPDRS - At the start of treatment with safinamide. Another BS/CDM verified 100% of computed variables for UPDRS score with respect to the algorithms described in the Statistical Analysis Plan (SAP).
- Psychiatric concomitant conditions and symptoms at the start of treatment with safinamide by patient age. The number and percentages of table variables (concomitant conditions) were verified by another BS/CDM.
- Clinically relevant non-psychiatric medical conditions at the start of treatment with safinamide. The number and percentages of table variables were verified by another BS/CDM.
- Safinamide initial administered daily dose. CDM verified 100% of variables with respect to the algorithms described in the SAP.
- Percentage of patients with safinamide dose change during observation period. CDM verified 100% of computed variables with respect to the algorithms described in the SAP. Another BS/CDM verified the table independently with respect to raw output.
- Percentage of patients with safinamide temporary interruption. CDM verified 100% of computed variables with respect to the algorithms described in the SAP.
- Previous and terminated PD treatments by patient age. CDM verified 100% of computed variables with respect to the algorithms described in the SAP.
- PD treatments ongoing at the start of safinamide treatment. CDM verified 100% of computed variables with respect to the algorithms described in the SAP.
- Concomitant use of psychiatric therapy to safinamide during observation. CDM verified 100% of computed variables with respect to the algorithms described in the SAP.
- Safinamide non-appropriate use. BS verified 100% of computed variables with respect to the algorithms described in the SAP. Another BS/CDM verified the table independently with respect to raw output.

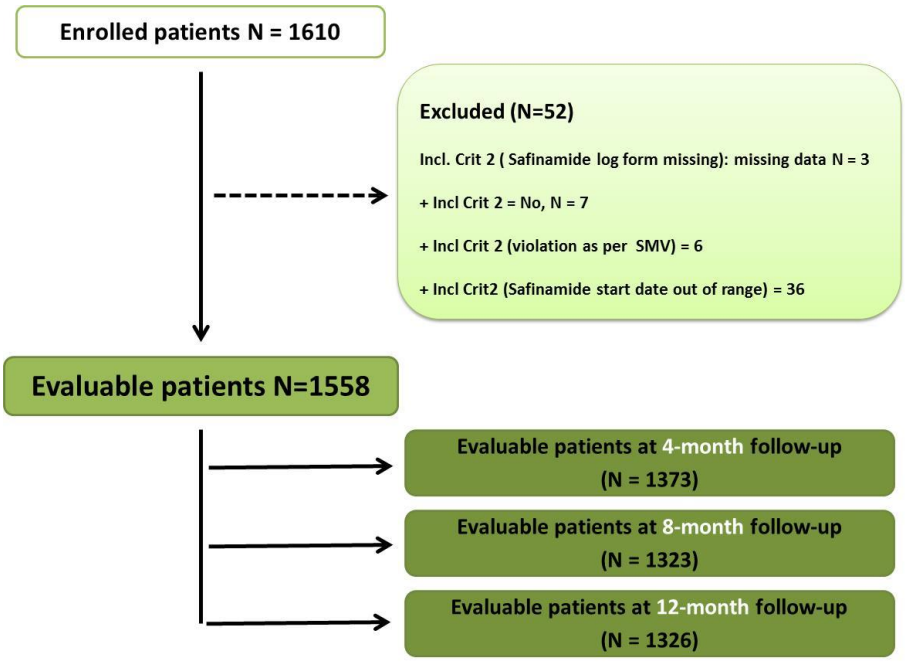
- Safinamide non-appropriate use during observation (derived). BS verified 20% of computed variables with respect to the algorithms described in the SAP.
- Adverse events, adverse reactions during observation. CDM verified 100% of computed variables with respect to the algorithms described in the SAP.
- Adverse events, adverse reactions during observation - Incidence Rate (IR). Another BS verified 100% of computed variables with respect to the algorithms described in the SAP (number of events and person-time).
- Special safety situations during observation period. CDM verified 100% of computed variables with respect to the algorithms described in the SAP.
- Description of special safety situations during observation. Another BS verified the table independently with respect to raw output.
- Description of adverse events during observation by seriousness (AE-based analysis). Another BS verified the table independently with respect to raw output.
- Description of adverse events during observation by seriousness classification criteria (AE-based analysis). Another BS verified the table independently with respect to raw output.

10. Results

10.1. Participants

As shown in **Figure 10.1:1**, 1610 patients were enrolled in the SYNAPSES study, and 1558 (96.8%) were evaluable for the analysis. Reasons for non-eligibility are shown in the diagram. Starting from evaluable patients, 1373 (85.3%), 1323 (82.2%) and 1326 (82.4%) were evaluable at 4-, 8- and 12-month follow up visits, respectively.

Figure 10.1:1 Patient's disposition



The proportion of patients evaluable at each follow-up did not vary significantly per country (as reported in Table 10.1.1), with Belgium and UK with the highest drop-out. Concerning UK the discrepancy observed between 4-month/8-month follow-ups and 12-month follow-up was due to a different frequency of visits as per normal clinical practice. In some sites involved, visits are usually performed every 6 months as per normal clinical practice.

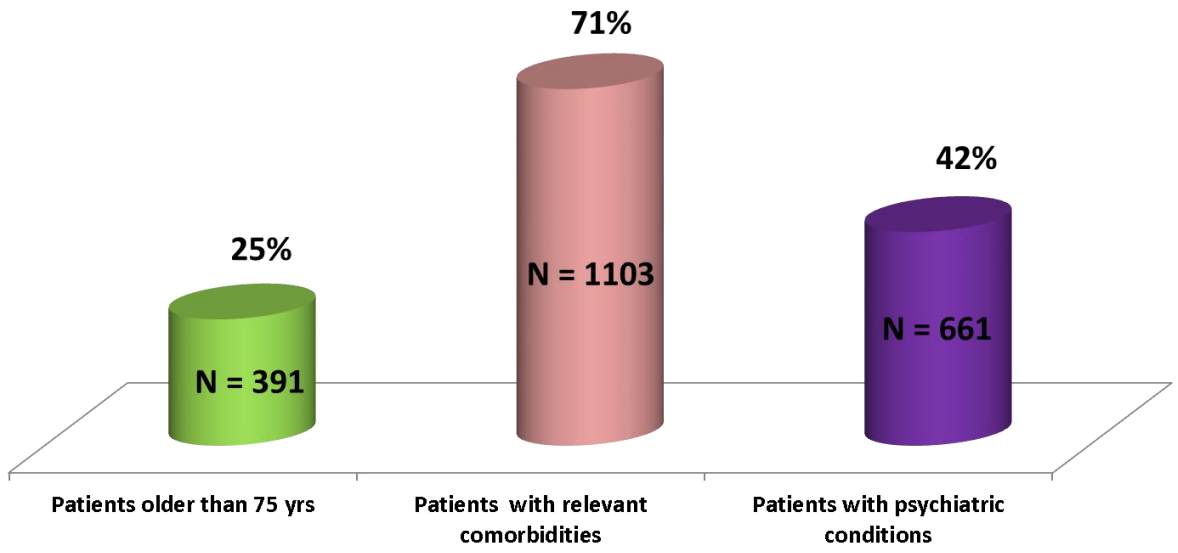
Table 10.1.1. Number patients at study visit and proportion at follow-up visits with respect to evaluable patients at enrolment.

	Total number of evaluable patients	Total evaluable patients at 4 months		Total evaluable patients at 8 months		Total evaluable patients at 12 months	
	N	N	%	N	%	N	%
Belgium	168	135	80.4	141	83.9	125	74.4
Germany	181	160	88.4	147	81.2	149	82.3
Italy	589	543	92.2	522	88.6	530	90.0
Spain	511	454	88.8	436	85.3	439	85.9
Switzerland	47	46	97.9	44	93.6	41	87.2
UK	62	35	56.5	33	53.2	42	67.7
Overall	1558	1373	88.1	1323	84.9	1326	85.1

As shown in **Figure 10.1:2**, starting from patients evaluable at baseline, for subgroup analyses the following populations were selected: patients older than 75 (N=391, 25.1%), patients with

relevant comorbidities (N=1103, 70.8%), patients with psychiatric conditions (N=661, 42.4%).

Figure 10.1:2 Subgroups of interest



10.2. Descriptive data

10.2.1. Socio-demographic characteristics at enrolment (overall and by subpopulations)

Detailed data for all socio-demographic characteristics at enrolment are shown in **Table 10.2.1: 1** (overall and separately in the subpopulations of patients older than 75, with relevant comorbidities and with psychiatric conditions). Males were 961 (61.7%) of the overall sample and mean (SD) age was 68.4 (9.7); 1543 out of 1558 patients (99%) were Caucasian. Considering patients without relevant comorbidities, they were approximately five years younger than patients with comorbidities (mean (SD) age: 64.6(10.7) vs 70.0(8.7) respectively). Considering, instead, patients without psychiatric conditions, there was no difference in age compared to patients with psychiatric conditions (mean (SD) age: 68.5 (9.9) vs 68.3 (9.4), respectively.

Table 10.2.1: 1 Socio-demographic characteristics at enrolment (overall and by target subpopulations)

		FAS (N= 1558)	aged > 75 yrs (N= 391)	pts with relevant comorbidities (N= 1103)	pts with psychiatric conditions (N= 661)
Gender (N, %)	Male	961 (61.7%)	221 (56.5%)	665 (60.3%)	356 (53.9%)
	Female	597 (38.3%)	170 (43.5%)	438 (39.7%)	305 (46.1%)

		FAS (N= 1558)	aged > 75 yrs (N= 391)	pts with relevant comorbidities (N= 1103)	pts with psychiatric conditions (N= 661)
Age at enrolment (years)	Mean (SD)	68.4 (9.7)	79.7 (3.1)	70.0 (8.7)	68.3 (9.4)
	Median	69.0	79.0	71.0	69.0
Race (N, %)	Caucasian	1543 (99.0%)	389 (99.5%)	1094 (99.2%)	658 (99.5%)

Note. Percentages were computed by column.

10.2.2. PD diagnosis and symptoms onset, disease severity at start of safinamide (overall and by subpopulations)

As shown in **Table 10.2.2: 1**, 1542 patients had a diagnosis of Idiopathic Parkinson's disease; on average (SD) 7.9 (5.3) years lapsed from PD diagnosis, 8.8 (5.5) years from PD onset of symptoms and the mean (SD) age at onset of symptoms was 59.3 (11.0) years. In the table, descriptive statistics by subpopulations were reported.

Table 10.2.2:1 PD diagnosis and symptom onset (overall and by target subpopulations)

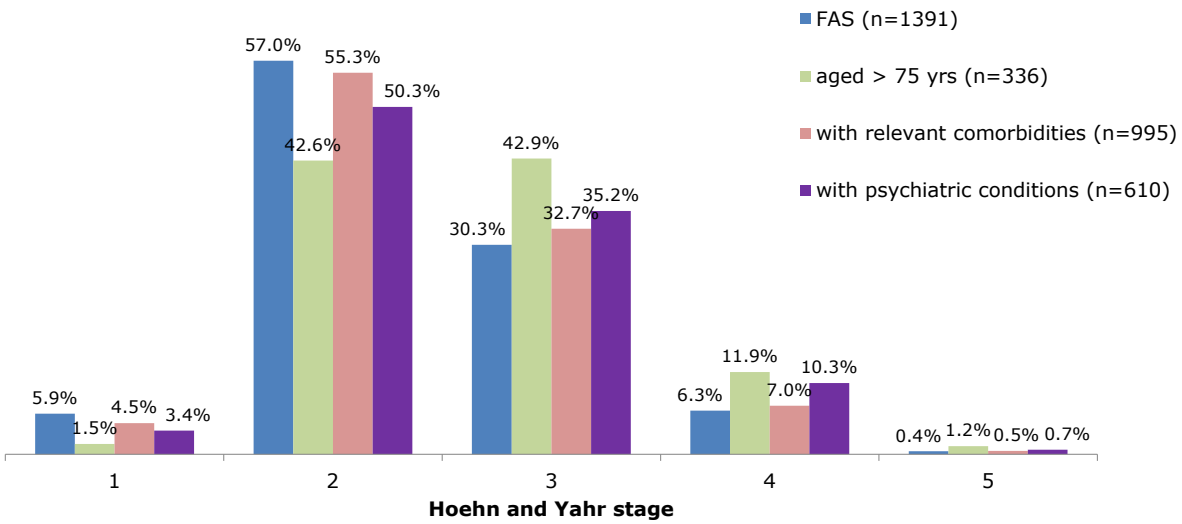
		FAS (N= 1558)	Aged > 75 yrs (N= 391)	pts with relevant comorbidities (N= 1103)	pts with psychiatric conditions (N= 661)
Diagnosis (N, %)	Idiopathic PD	1542 (99.0%)	389 (99.5%)	1094 (99.2%)	653 (98.8%)
	Atypical Parkinsonisms	12 (0.8%)	2 (0.5%)	7 (0.6%)	6 (0.9%)
	Other	4 (0.3%)	0 (0.0%)	2 (0.2%)	2 (0.3%)
Time from PD diagnosis (years): mean (SD)		7.9 (5.3)	7.9 (5.3)	7.8 (5.3)	8.4 (5.5)
Time from PD onset of symptoms (years): mean (SD)		8.8 (5.5)	8.9 (5.5)	8.7 (5.4)	9.3 (5.5)
Age at onset of symptoms (years): mean (SD)		59.3 (11.0)	70.9 (6.5)	61.0 (10.1)	58.8 (10.7)

Note. Percentages were computed by column.
PD: Parkinson's Disease.
Patients with other diagnosis (N=4) had Juvenile Parkinsons' disease.

Figure 10.2.2: 1 shows the distribution of patients according to Hoehn and Yahr stage at the start of treatment with safinamide: overall 37.1% (N=516) of patients had H&Y stage > 2, while in the subpopulations the proportions were 56.0% (patients aged > 75, N=188), 40.2% (patients with relevant comorbidities, N=400) and 46.2% (patients with psychiatric conditions,

N=282).

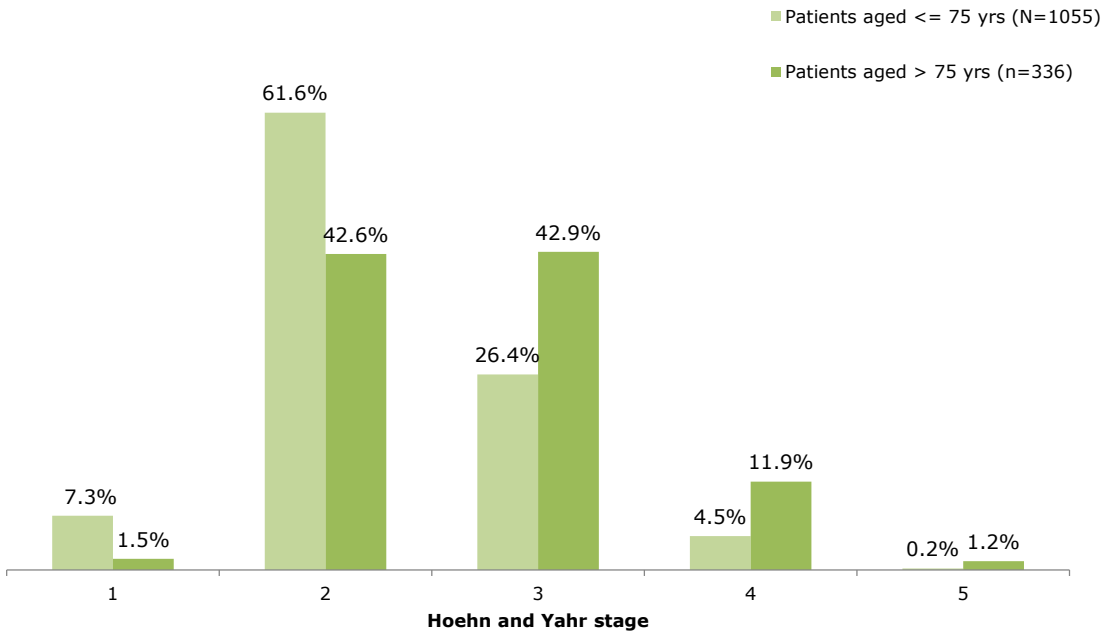
Figure 10.2.2:1 H&Y at the start of treatment with safinamide (overall and by subpopulations)



Note. Percentages were computed within each group.

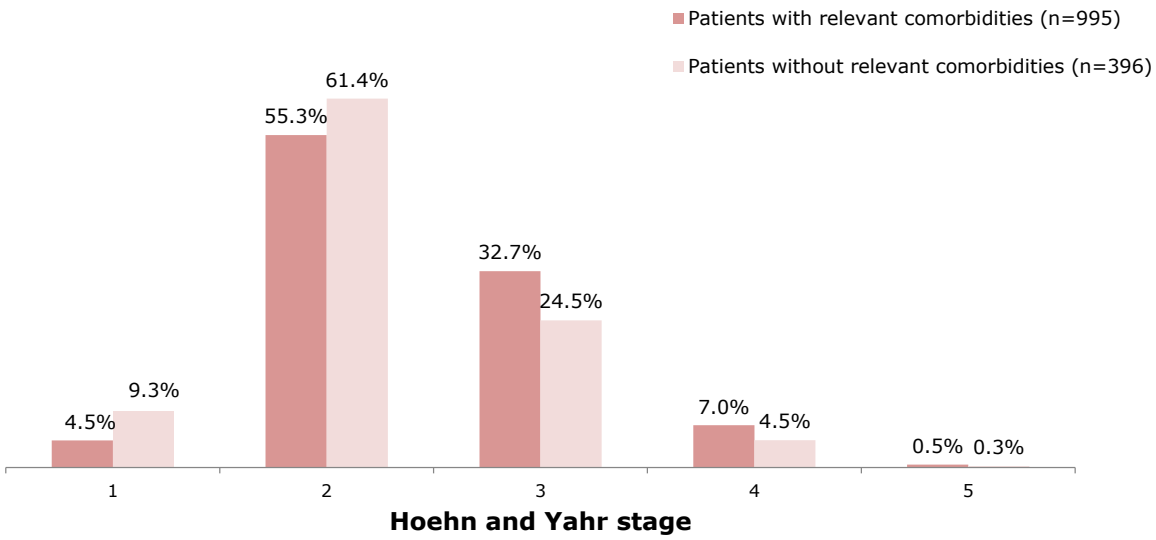
As shown in **Figures 10.2.2:2, 3, 4,** lower H&Y stages were observed for younger patients (vs older ones), for patients without (vs patients with) relevant comorbidities and for patients without (vs patients with) psychiatric conditions.

Figure 10.2.2:2 H&Y at the start of treatment with safinamide (patients aged ≤75 vs >75 years)



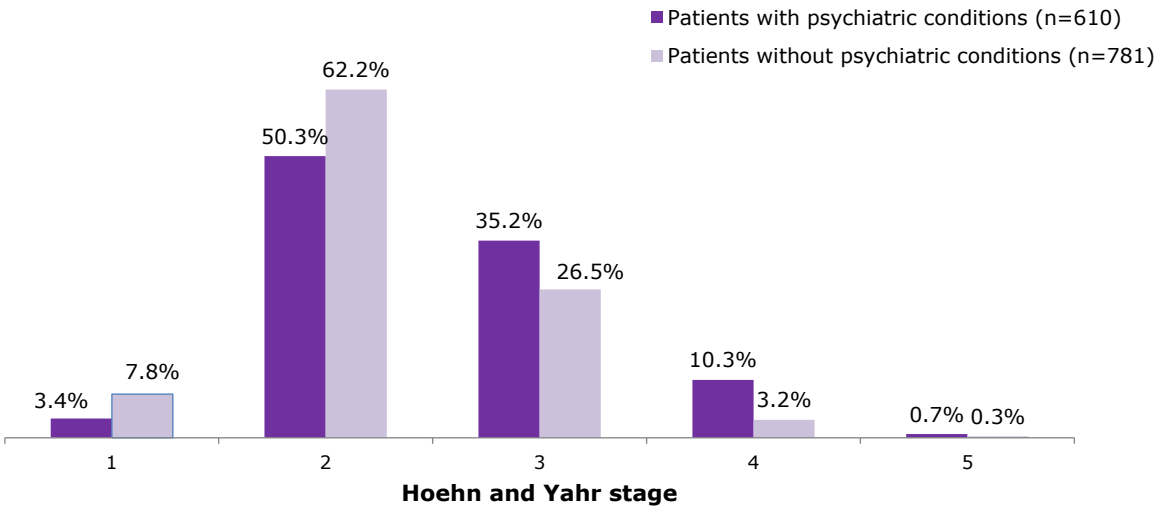
Note. Percentages were computed within each group.

Figure 10.2.2:3 H&Y at the start of treatment with safinamide (patients with vs without relevant comorbidities)



Note. Percentages were computed within each group.

Figure 10.2.2:4 H&Y at the start of treatment with safinamide (patients with vs without psychiatric conditions)



Note. Percentages were computed within each group.

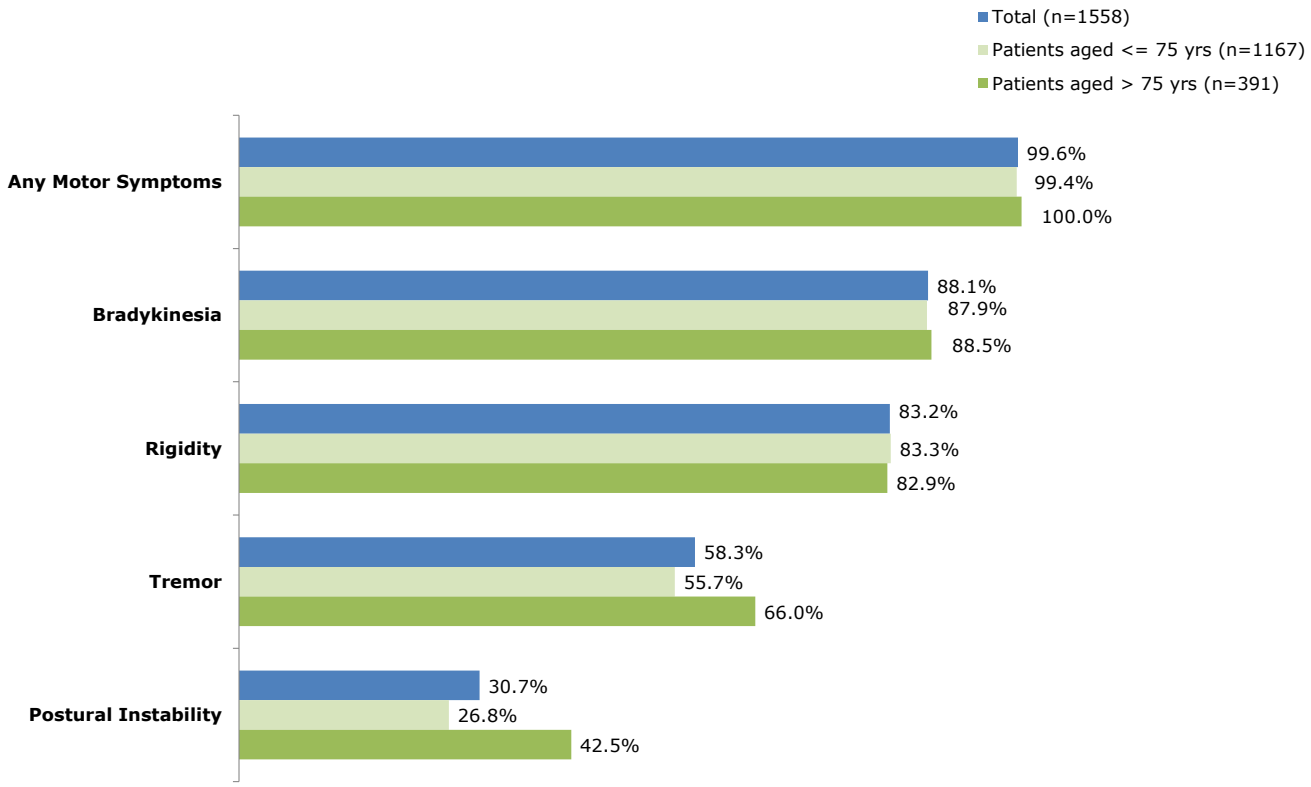
At the start of treatment with safinamide, dementia was diagnosed in 30 patients (1.9%), 12 (3.1%) of them aged > 75, 22 (2.0%) with relevant comorbidities, and 22 (3.3%) suffering from psychiatric conditions.

10.2.3. Motor and Non-motor symptoms at start of safinamide (overall and by subpopulations)

At the start of treatment, 1551 (99.6%) patients had motor symptoms and 1380 (88.6%) had Non Motor Symptoms (NMSs). As regards motor symptoms, as shown in **Figure 10.2.3:1** and **Figure 10.2.3:2**, tremor was more frequent in patients aged >75 than ≤ 75 years (n=258,

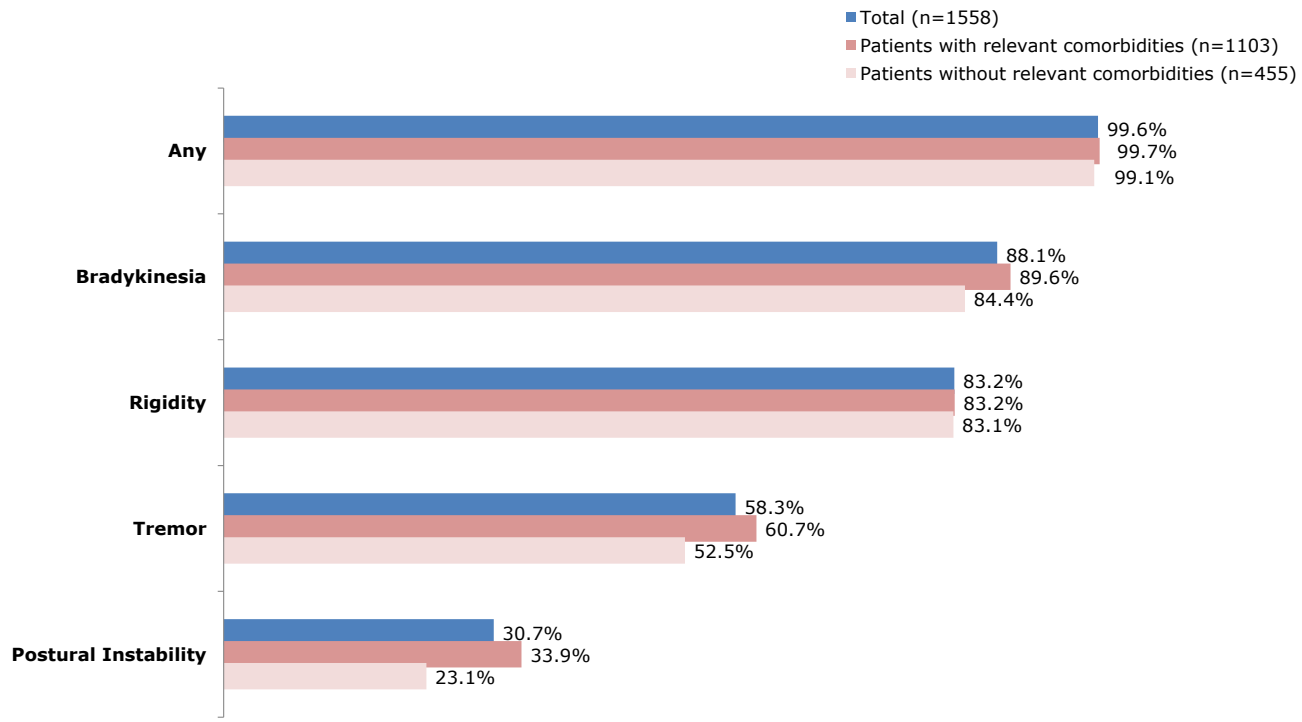
66% vs N=650, 55.7%, respectively) and in patients with than without relevant comorbidities (N=669, 60.7% vs N=239, 52.5%, respectively).
Postural instability was more frequent in patients aged >75 than in ≤ 75 years (N=166, 42.5% vs N=313, 26.8%, respectively), in patients with than without relevant comorbidities (N=374, 33.9% vs N=105, 23.1%, respectively) and also in patients with (N=256, 38.7%) vs without (N=223, 24.9%) psychiatric conditions (see **Figure 10.2.3: 3**).

Figure 10.2.3:1 Frequency of Motor Symptoms at the start of treatment with safinamide vs age (overall and patients aged ≤75 vs >75 years)



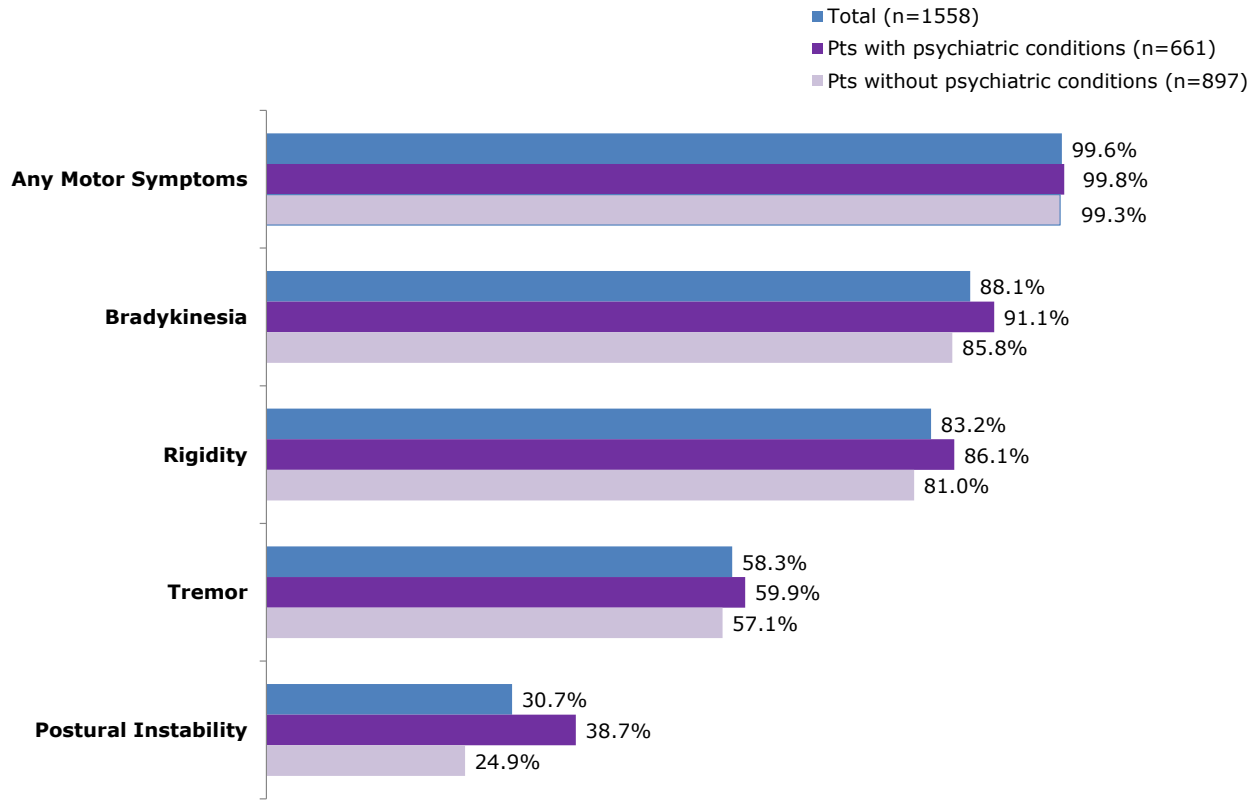
Note. Percentages were computed within each group.

Figure 10.2.3:2 Frequency of Motor Symptoms at the start of treatment with safinamide vs relevant comorbidities (overall and patients with vs without relevant comorbidities)



Note. Percentages were computed within each group.

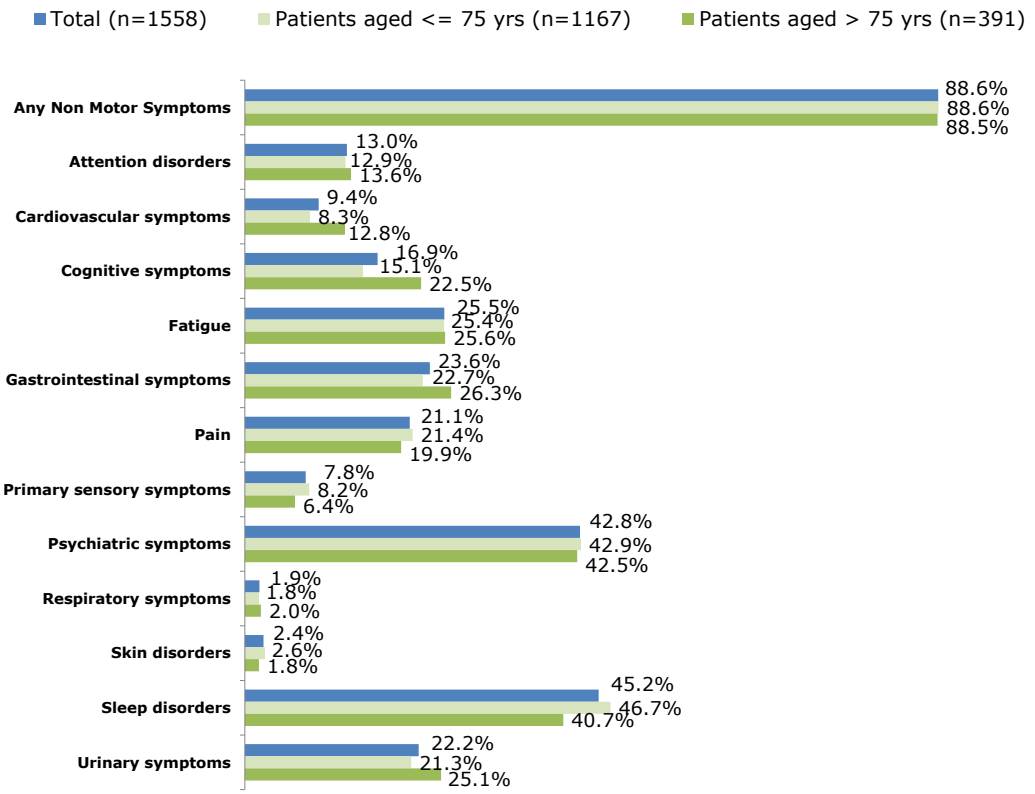
Figure 10.2.3:3 Frequency of Motor Symptoms at the start of treatment with safinamide vs psychiatric conditions (overall and patients with vs without psychiatric conditions)



Note. Percentages were computed within each group.

Figures 10.2.3: 4 shows the distribution of patients according to NMSs at start of treatment overall and by age subpopulation: cognitive symptoms were more frequent in patients aged >75 than ≤ 75 (N=88, 22.5% vs N=176, 15.1%, respectively). Also cardiovascular, gastrointestinal and urinary symptoms, were more frequent in patients aged >75 (12.8% (N=50), 26.3% (N=103), 25.1% (N=98), respectively) than ≤ 75 (8.3% (N=97), 22.7% (N=265), 21.3% (N=248), respectively). On the other hand, sleep disorders were more frequent in patients aged ≤ 75 (N=545, 46.7%) than in older ones (N=159, 40.7%).

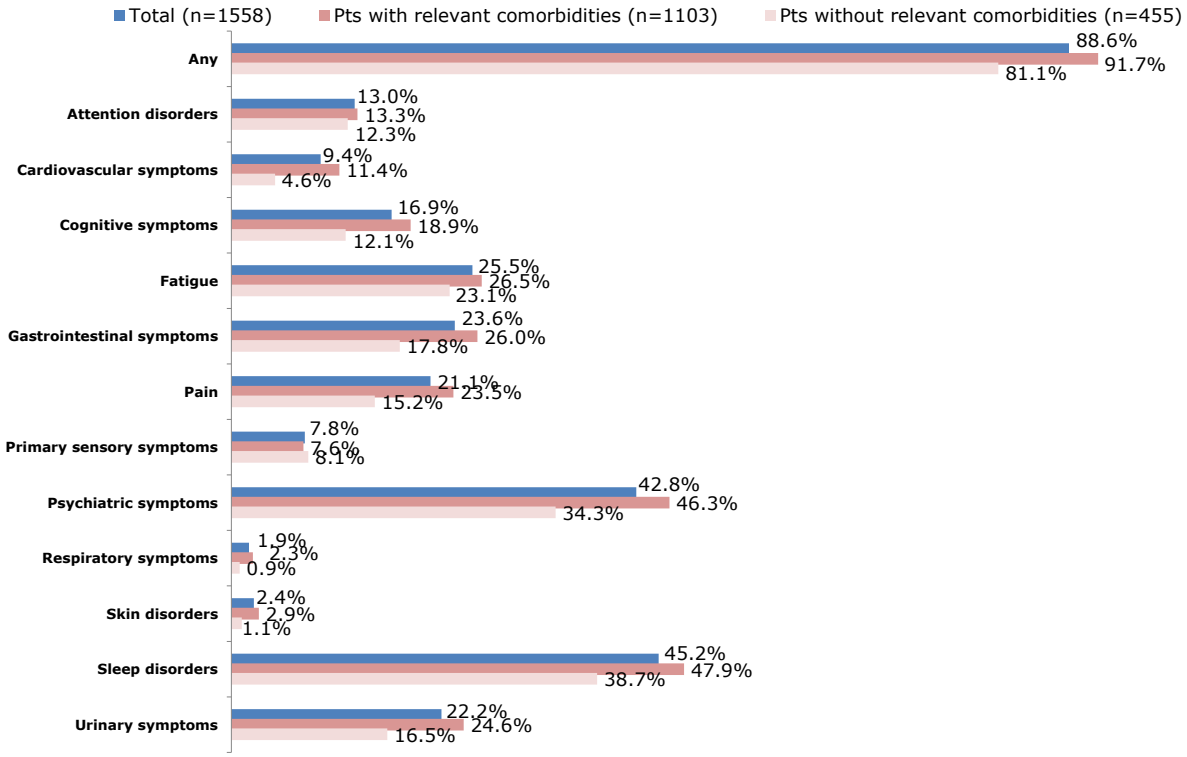
Figure 10.2.3:4 Frequency of Non-Motor Symptoms at the start of safinamide treatment (overall and by patient age)



Note. Percentages were computed within each group.

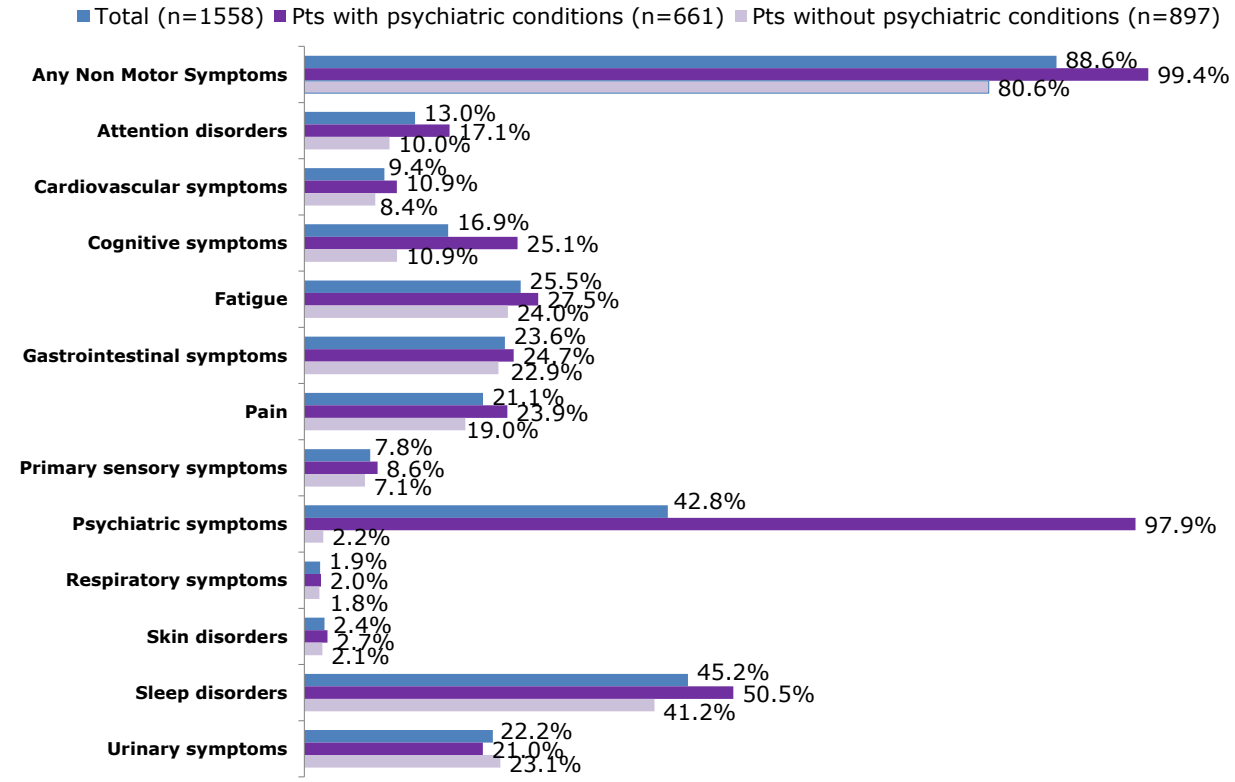
As shown in **Figure 10.2.3: 5** and **Figure 10.2.3: 6** almost all non-motor symptoms were more frequent in patients with relevant comorbidities and with psychiatric conditions than in those without comorbidities/psychiatric conditions.

Figure 10.2.3:5 Frequency of Non Motor Symptoms at the start of safinamide treatment (overall and patients with/without relevant comorbidities)



Note. Percentages were computed within each group.

Figure 10.2.3:6 Frequency of Non-Motor Symptoms at the start of safinamide treatment (overall and patients with/without psychiatric conditions)

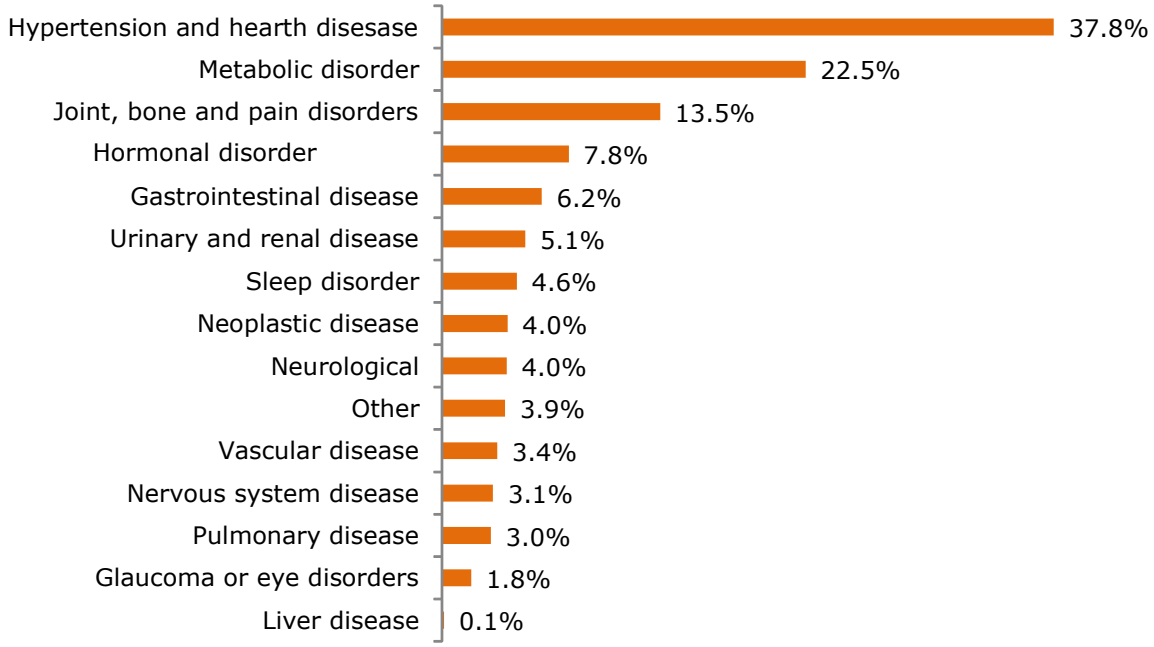


Note. Percentages were computed within each group.

10.2.4. Relevant comorbidities and psychiatric conditions at start of safinamide

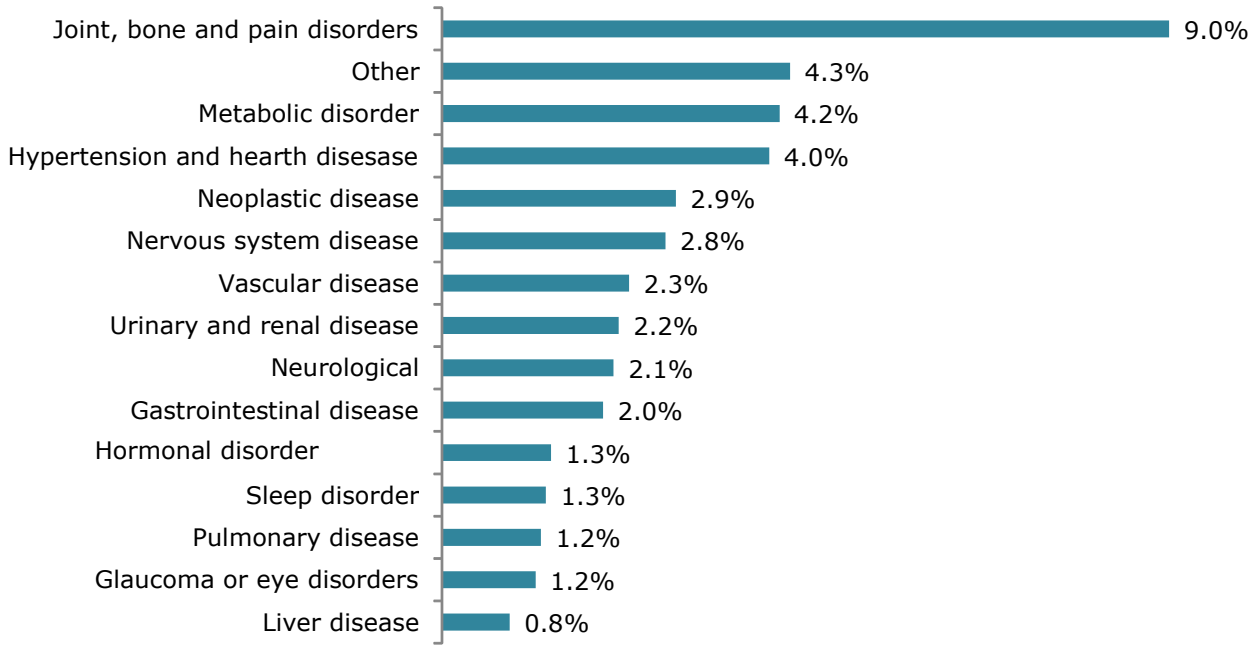
At the start of safinamide treatment, patients suffering from clinically relevant non psychiatric condition were 1103 (70.8%), of whom 1001 (90.8%) were on treatment. **Figures 10.2.4: 1** and **10.2.4: 2** show the distribution of relevant treated and not-treated comorbidities, respectively. Among the treated comorbidities, the most frequent (>10%) were hypertension and heart disease (N=589, 37.8%), metabolic disorders (N=350, 22.5%) and joint, bone and pain disorders (N=210, 13.5%). No relevant non-treated comorbidities had higher-than-10% frequency (see **Figure 10.2.4: 2**).

Figure 10.2.4:1 Frequency of relevant treated comorbidities (overall)



Note. Percentages were computed out of total number of evaluable patients (N=1558).

Figure 10.2.4:2 Frequency of relevant non-treated comorbidities (overall)



Note. Percentages were computed out of total number of evaluable patients (N=1558).

At the start of safinamide treatment, 661 (42.4%) patients reported psychiatric conditions and 663 (42.6%) patients reported psychiatric symptoms. Psychiatric symptoms were reported by patient and assessed by the clinician, psychiatric conditions were assessed as a diagnosis by the neurologist. As shown in **Table 10.2.4:1**, the most frequently reported symptoms were depression (27.9%) and anxiety (15.4%) and, among psychiatric conditions, anxiety (14.8%)and major depression (12.6%).

Table 10.2.4: 1 Psychiatric conditions and symptoms at the start of safinamide (overall)

		FAS (N= 1558)
Psychiatric symptoms (N, %)	Depression	435 (27.9%)
	Anxiety	240 (15.4%)
	Behavioural disturbs*	137 (8.8%)
	Apathy	73 (4.7%)
	Other	65 (4.2%)
Psychiatric conditions (N, %)	Other	342 (22.0%)
	Anxiety	230 (14.8%)
	Major depression	196 (12.6%)
	Psychosis	37 (2.4%)
	Bipolar disorder	5 (0.3%)

Note. Percentages were computed by column.
Note. Among psychiatric conditions in class "Other", the most frequently reported (N>10) were: depression (N=68), mild depression (N=40), apathy (N=33), minor depression (N=30), hallucinations

(N=28), insomnia (N=24), impulse control disorder (N=22) and depressive symptoms (N=18).
*e.g. psychosis, impulse control disorder, hallucinations.

10.2.5. Fluctuations and UPDRS at start of safinamide treatment

At safinamide treatment start, 1437 (92.2%) patients had fluctuations, the most frequent ones being wearing off (1158, 74.3%) and dyskinesia (610, 39.2%). **Table 10.2.5: 1** includes details of occurred fluctuations at the start of safinamide.

Table 10.2.5: 1 Fluctuations at the start of treatment with safinamide (overall)

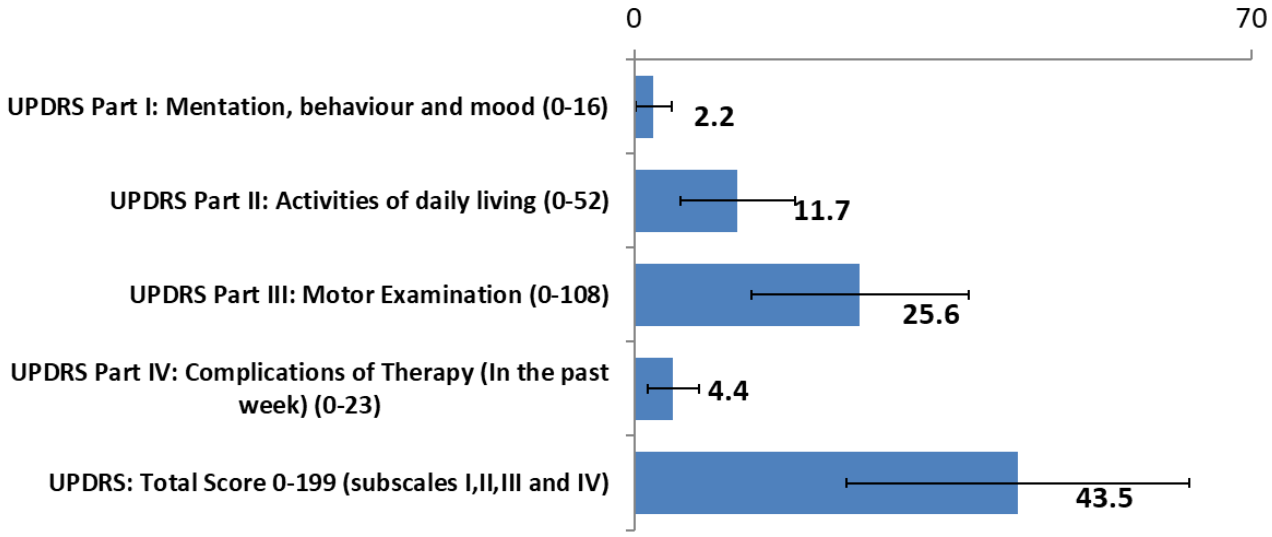
		FAS (N= 1558)
Fluctuations	Any	1437 (92.2%)
	Wearing off	1158 (74.3%)
	Unpredictable	264 (16.9%)
	Early morning fluctuations	363 (23.3%)
	Delayed on fluctuation	177 (11.4%)
	Dyskinesia	610 (39.2%)
	Other	87 (5.6%)

Note. Percentages were computed out of the number of evaluable patients.

Fluctuations were present in 1079 (92.5%) and 358 (91.6%) patients aged ≤75 and > 75, respectively.

Mean (SD) UPDRS (part I, II, III, IV and total) scores are shown in **Figure 10.2.5: 1**, showing disease severity at start of treatement.

Figure 10.2.5: 1 UPDRS (part I, II, III, IV, total) scores at the start of treatment with safinamide (mean (SD))



10.2.6. Fluctuations and UPDRS during observation

At 4, 8 and 12 months after start of safinamide treatment, 1009 (73.5%), 934 (70.6%) and 894 (67.4%) patients had fluctuations, the more frequent ones being wearing off and dyskinesia. **Table 10.2.6: 1** shows the details of fluctuations during observation.

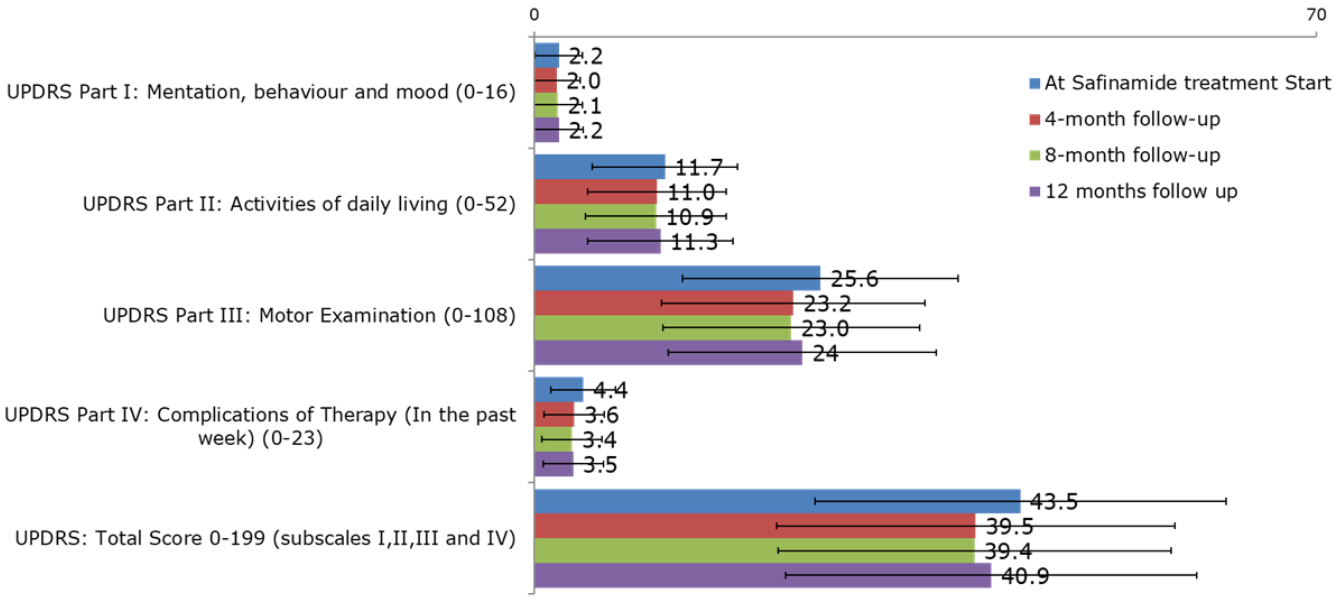
Table 10.2.6: 1 Fluctuations during observation (overall)

		Total evaluable patients at 4 months (N= 1373)	Total evaluable patients at 8 months (N= 1323)	Total evaluable patients at 12 months (N= 1326)
Fluctuations	Any	1009 (73.5%)	934 (70.6%)	894 (67.4%)
	Wearing off	752 (54.8%)	704 (53.2%)	701 (52.9%)
	Unpredictable	152 (11.1%)	149 (11.3%)	133 (10.0%)
	Early morning fluctuations	198 (14.4%)	196 (14.8%)	182 (13.7%)
	Delayed on fluctuation	108 (7.9%)	109 (8.2%)	109 (8.2%)
	Dyskinesia	469 (34.2%)	409 (30.9%)	369 (27.8%)
	Other	62 (4.5%)	52 (3.9%)	32 (2.4%)

Note. Percentages were computed out of the number of patients evaluable for the FAS and for each follow up visit.

Figure 10.2.6: 1 depicts the mean (SD) of UPDRS (part I, II, III, IV, total) scores at the beginning of treatment with safinamide and at 4-, 8-, 12-month follow up. A substantial stability of disease severity over time emerged.

Figure 10.2.6: 1 UPDRS (part I, II, III, IV, total scores) at start of treatment with safinamide and at 4-, 8-, 12-month follow up (overall)



Note. Mean (SD) were shown.

Note. Percentages were computed out of the total number of evaluable patients for the FAS and at each follow up visit with UPDRS filled in and available change.
Note. The difference between UPDRS scores at follow-up and the baseline was computed.

10.2.7. Terminated PD treatments at start of safinamide treatment (overall)

Almost one fifth of evaluable patients (N=310, 19.9%) terminated PD treatments before starting safinamide treatment.
Two-hundred-eighty-two patients (18.1%) had a previous treatment with MAO inhibitors, 31 (2.0%) patients with levodopa, 15 (1.0%) patients with dopamine agonist, 14 (0.9%) patients with COMT inhibitors.
Distribution of patients according to previous PD treatment that was terminated before starting safinamide treatment (overall) is shown in **Table 10.2.7: 1**.

Table 10.2.7: 1 Previous and terminated PD treatments (overall)

Categories	Active	FAS (N= 1558)
≥ 1 previous terminated PD treatment	Any	310 (19.9%)
Amantadine	**Any**	**1 (0.1%)**
	Amantadine hydrochloride	1 (0.1%)
Anticolinergics	**Any**	**1 (0.1%)**
	Trihexyphenidyl hydrochloride	1 (0.1%)
COMT inhibitors	**Any**	**14 (0.9%)**

Categories	Active	FAS (N= 1558)
	Carbidopa - Entacapone - Levodopa	11 (0.7%)
	Opicapone	3 (0.2%)
Dopamine agonists	**Any**	**15 (1.0%)**
	Apomorphine hydrochloride	1 (0.1%)
	Pramipexole	5 (0.3%)
	Pramipexole dihydrochloride	4 (0.3%)
	Ropinirole hydrochloride	1 (0.1%)
	Rotigotine	4 (0.3%)
Levodopa	**Any**	**31 (2.0%)**
	Benserazide hydrochloride - Levodopa	10 (0.6%)
	Carbidopa - Levodopa	9 (0.6%)
	Carbidopa - Melevodopa	2 (0.1%)
	Carbidopa - Entacapone - Levodopa	11 (0.7%)
	Carbidopa Monohydrate - Levodopa	2 (0.1%)
MAO inhibitors	**Any**	**282 (18.1%)**
	Rasagiline	42 (2.7%)
	Rasagiline mesylate	205 (13.2%)
	Rasagiline tartrate	2 (0.1%)
	Selegiline hydrochloride	34 (2.2%)

Note. Percentages were computed out of the total number of patients evaluable for the FAS. A patient could have had more than one previous and terminated PD treatment.
Note. Carbidopa-Entacapone-Levodopa is shown both as Levodopa and as COMT inhibitors

10.3. Outcome data

The results of the primary and secondary endpoints are reported in the following section.

10.4. Main results

10.4.1 Primary Endpoint(s)/Outcome(s)

10.4.1.1. Adverse events

As reported in **Table 10.4.1.1:1**, during observation 714 (45.8%) patients experienced in total 1435 AEs and 432 (27.7%) patients experienced in total 685 ADRs.
One-hundred-forty-three patients (9.2%) had at least one SAE during observation and 36 patients (2.3%) at least one SADR. The total number of SAEs and SADRs were 194 and 48, respectively.
The monthly incidence rates of events (AEs, SAEs, ADRs and SADRs) observed during the study are shown in **Table 10.4.1.1:2**.

Table 10.4.1.1: 1 Adverse events and adverse reactions during observation (overall)

	FAS (N= 1558)
Patients with at least one AE (N, %)	714 (45.8%)
Patients with at least one SAE (N, %)	143 (9.2%)
Patients with at least one ADR (N, %)	432 (27.7%)
Patients with at least one SADR (N, %)	36 (2.3%)
Total number of AEs (N)	1435
Total number of SAEs (N)	194
Total number of ADRs (N)	685
Total number of SADRs (N)	48

AE: Adverse Event. ADR: Adverse Drug Reaction. SADR: Serious Adverse Drug Reaction. SAE: Serious Adverse Event.

The monthly incidence rate of AE, SAE, ADR and SADR is reported in Table 10.4.1.1:2. Every 100 patients observed during one month 7.95 AEs occurred.

Table 10.4.1.1: 2 Monthly Incidence Rate (IR) of adverse events and adverse reactions during observation (overall)

	Monthly Incidence Rate (IR) (95% CI)
AEs	7.95% (7.55-8.37%)
SAEs	1.07% (0.93-1.24%)
ADRs	3.79% (3.52-4.09%)
SADRs	0.27% (0.20-0.35%)

AE: Adverse Event. ADR: Adverse Drug Reaction. SADR: Serious Adverse Drug Reaction. SAE: Serious Adverse Event.

As for severity, adverse events were mainly mild (N=888, 61.9%). Moderate and severe AEs were 404 (28.2%) and 143 (10.0%), respectively. One third of adverse events (N=480, 33.4%) were nervous system disorders and 14.3% of AEs (N=205) were psychiatric disorders.
Among nervous system disorders, the most frequently reported AEs were dyskinesia (N=197, 13.7% of total number of AEs) and dizziness (N=39, 2.7%), while among psychiatric disorders, hallucinations were the most frequently reported (N=41, 2.9%).
Forty-four (3.1%) eye disorders were observed (all of them were non serious); the most frequent ones were blurred vision (9 AE, 0.6%), reduced visual acuity (6 AE, 0.4%), diplopia (6 AE, 0.4%) and visual impairment (4 AE, 0.3%).
Table 10.4.1.1: 3 shows the distribution of adverse events severity by System Organ Class. The detailed distribution of adverse events severity by SOC and PT is reported in Table 35 of Final Statistical Report (see Annex 1 - 6 Final Statistical Report).

Table 10.4.1.1: 3 Description of adverse events during observation by severity expressed as System Organ Class (AE-based analysis) (overall)

	Any	Mild	Moderate	Severe
Total N of AEs occurred during study	1435 (100.0%)	888 (61.9%)	404 (28.2%)	143 (10.0%)
System Organ Class				
Nervous system disorders	480 (33.4%)	345 (24.0%)	110 (7.7%)	25 (1.7%)
Psychiatric disorders	205 (14.3%)	121 (8.4%)	68 (4.7%)	16 (1.1%)
Gastrointestinal disorders	107 (7.5%)	73 (5.1%)	29 (2.0%)	5 (0.3%)
Injury, poisoning and procedural complications	99 (6.9%)	36 (2.5%)	41 (2.9%)	22 (1.5%)
Musculoskeletal and connective tissue disorders	94 (6.6%)	55 (3.8%)	37 (2.6%)	2 (0.1%)
General disorders and administration site conditions	93 (6.5%)	65 (4.5%)	21 (1.5%)	7 (0.5%)
Infections and infestations	75 (5.2%)	32 (2.2%)	18 (1.3%)	25 (1.7%)
Eye disorders	44 (3.1%)	34 (2.4%)	10 (0.7%)	0 (0%)
Vascular disorders	37 (2.6%)	23 (1.6%)	12 (0.8%)	2 (0.1%)
Respiratory, thoracic and mediastinal disorders	32 (2.2%)	16 (1.1%)	8 (0.6%)	8 (0.6%)
Skin and subcutaneous tissue disorders	27 (1.9%)	22 (1.5%)	4 (0.3%)	1 (0.1%)
Renal and urinary disorders	26 (1.8%)	16 (1.1%)	7 (0.5%)	3 (0.2%)
Cardiac disorders	25 (1.7%)	5 (0.3%)	9 (0.6%)	11 (0.8%)
Metabolism and nutrition disorders	18 (1.3%)	12 (0.8%)	4 (0.3%)	2 (0.1%)
Investigations	12 (0.8%)	9 (0.6%)	3 (0.2%)	0 (0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	12 (0.8%)	1 (0.1%)	3 (0.2%)	8 (0.6%)
Surgical and medical procedures	12 (0.8%)	3 (0.2%)	7 (0.5%)	2 (0.1%)
Ear and labyrinth disorders	11 (0.8%)	11 (0.8%)	0 (0%)	0 (0%)
Hepatobiliary disorders	7 (0.5%)	0 (0.0%)	6 (0.4%)	1 (0.1%)
Blood and lymphatic system disorders	6 (0.4%)	3 (0.2%)	2 (0.1%)	1 (0.1%)
Social circumstances	6 (0.4%)	2 (0.1%)	3 (0.2%)	1 (0.1%)
Reproductive system and breast disorders	5 (0.3%)	3 (0.2%)	1 (0.1%)	1 (0.1%)
Endocrine disorders	2 (0.1%)	1 (0.1%)	1 (0.1%)	0 (0%)

Note. Percentages were computed out of the total number of AE.
Note. Data sorted by descending frequency of SOC.
AE: Adverse Event.

Considering the 1435 adverse events, 750 (52.3%) had no causal relationship with safinamide, while 135 (9.4%), 326 (22.7%), 193 (13.4%) and 29 (2.0%) had unlikely, possible, probable and definite causal relationship with safinamide respectively (two events had an unclassifiable relation).

Figure 10.4.1.1: 1 shows the distribution of 29 adverse events with a definite causal relationship with safinamide by PT.

Figure 10.4.1.1: 1 Adverse events with a definite causal relationship with safinamide by Preferred Term (N=29)

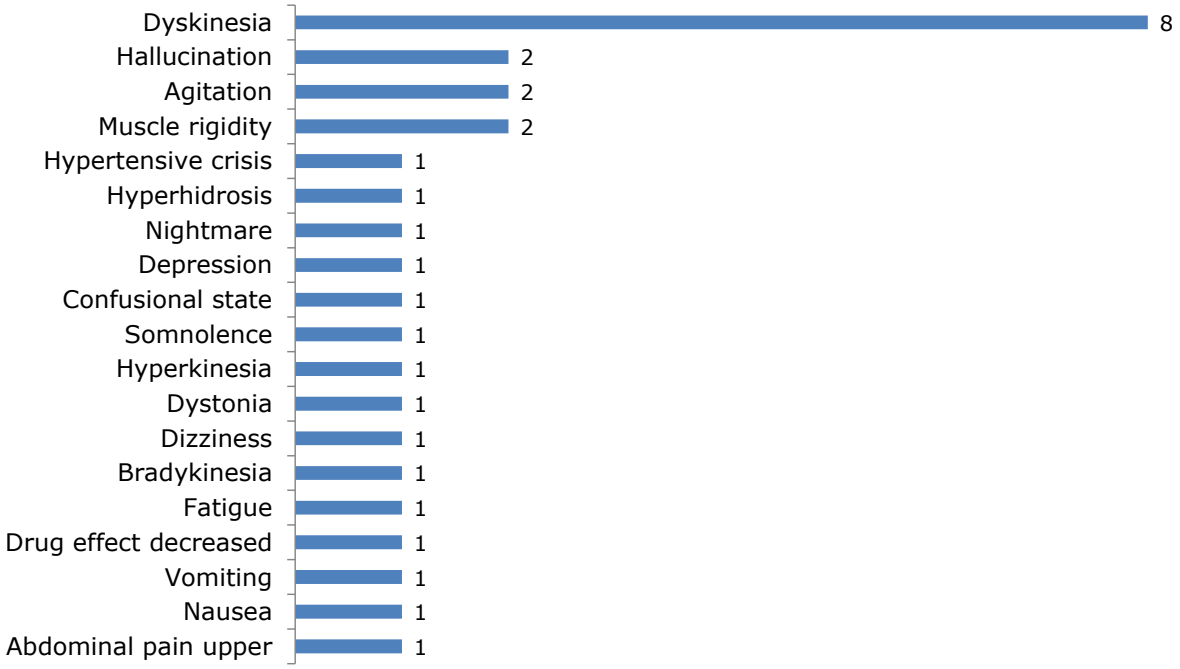
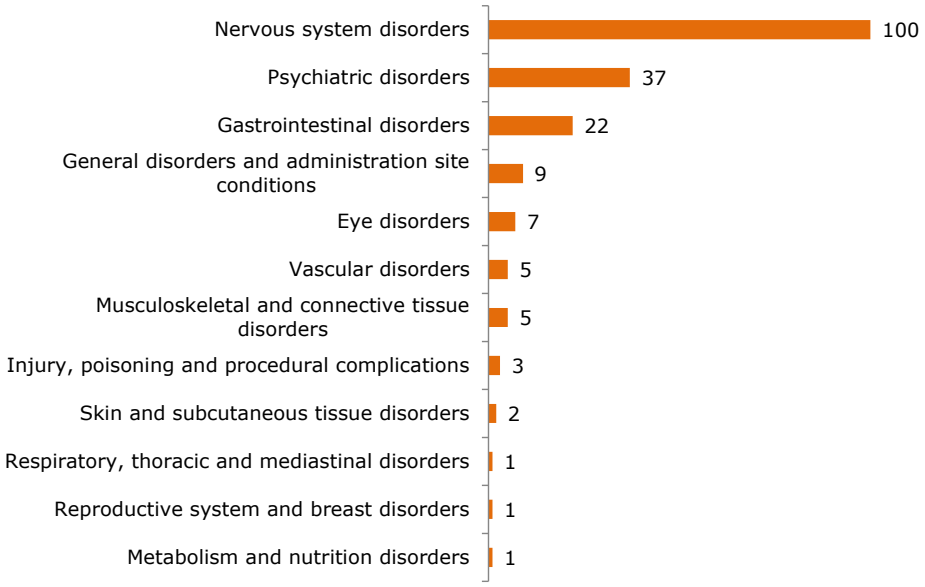


Figure 10.4.1.1: 2 and **Figure 10.4.1.1: 3** show the distribution of 193 and 326 AEs with a probable and possible causal relationship with safinamide by SOC.

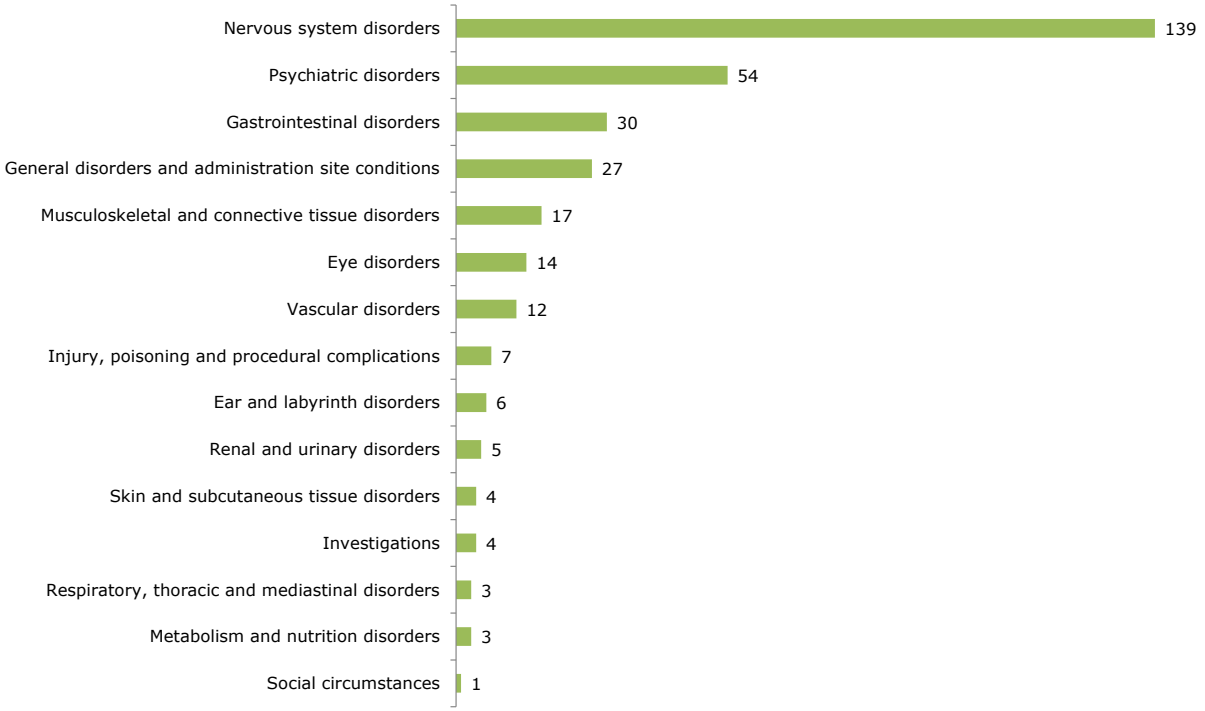
Among the AEs with a probable causal relationship with safinamide, considering the 100 (7%) belonging to Nervous system disorders SOC, the most frequently reported events were dyskinesia (N=55, 3.8%) and dizziness (N=13, 0.9%); considering instead the Psychiatric disorders, the most frequently reported events were anxiety (N=6, 0.4%) and hallucinations (N=5, 0.3%).

Figure 10.4.1.1: 2 Adverse events with a probable causal relationship with safinamide by System Organ Class (N=193)



Among AEs with a possible causal relationship with safinamide, considering 139 (9.7%) Nervous system disorders, the most frequently reported events were dyskinesia (N=65, 4.5%) and dizziness (N=16, 1.1%); considering instead psychiatric disorders (N=54, 3.8%), the most frequently reported events were hallucinations (N=12, 0.8%, of which 6, 0.4%, were visual hallucinations), anxiety (N=7, 0.5%) and insomnia (N=5, 0.3%).

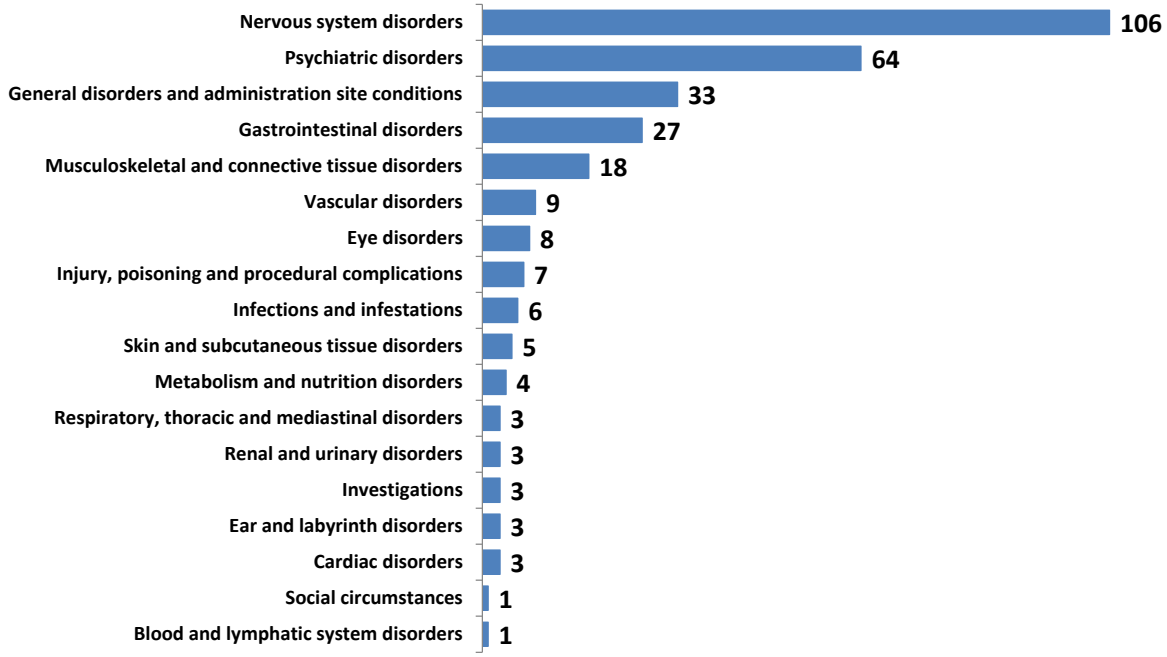
Figure 10.4.1.1: 3 Adverse events with a possible causal relationship with safinamide by System Organ Class (N=326)



Eye disorders with possible and probable relation with safinamide were 14 (1.0%) and 7 (0.5%) events, respectively. The latter were specifically: diplopia, eye pain, photopsia, blurred vision, reduced visual acuity, 2 visual impairments. The remaining were not related (N=22, 1.5%) or unlikely (N=1, 0.1%).
The detailed distribution of adverse events by causal relationship with safinamide is reported in Table 38 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).

For 993 AEs (69.2%) no action was taken; instead, drug was permanently interrupted for 304 (21.2%) adverse events, the dosage was reduced in 73 (5.1%) events and the drug was temporarily interrupted in 59 (4.1%) events.
The distribution of occurred adverse events by action taken in the overall sample is reported in Table 40 of Final Statistical Report (see Annex 1 - 6 Final Statistical Report); in the table events are classified by SOC and PT.
Figure 10.4.1.1: 4 shows the distribution of 304 AEs causing safinamide permanent discontinuation by SOC. The drug was permanently interrupted in 32 cases of dyskinesia, 18 cases of dizziness, 8 cases of agitation, 8 cases of confusional state, 8 cases of hallucination, 7 cases of headache, 6 asthenia, 6 gait disturbance, 6 malaise, 5 nausea, etc.

Figure 10.4.1.1: 4 Adverse events causing safinamide permanent discontinuation by System Organ Class (N=304)



The outcome of the 1435 occurred adverse events was as follows: recovered/resolved in 824 (57.4%) events, not recovered/not resolved in 330 (23.0%) events, recovering/resolving at the end of the observation in 132 (9.2%) events, fatal in 24 (1.7%) cases and recovered/resolved with sequelae in 17 (1.2%) cases.

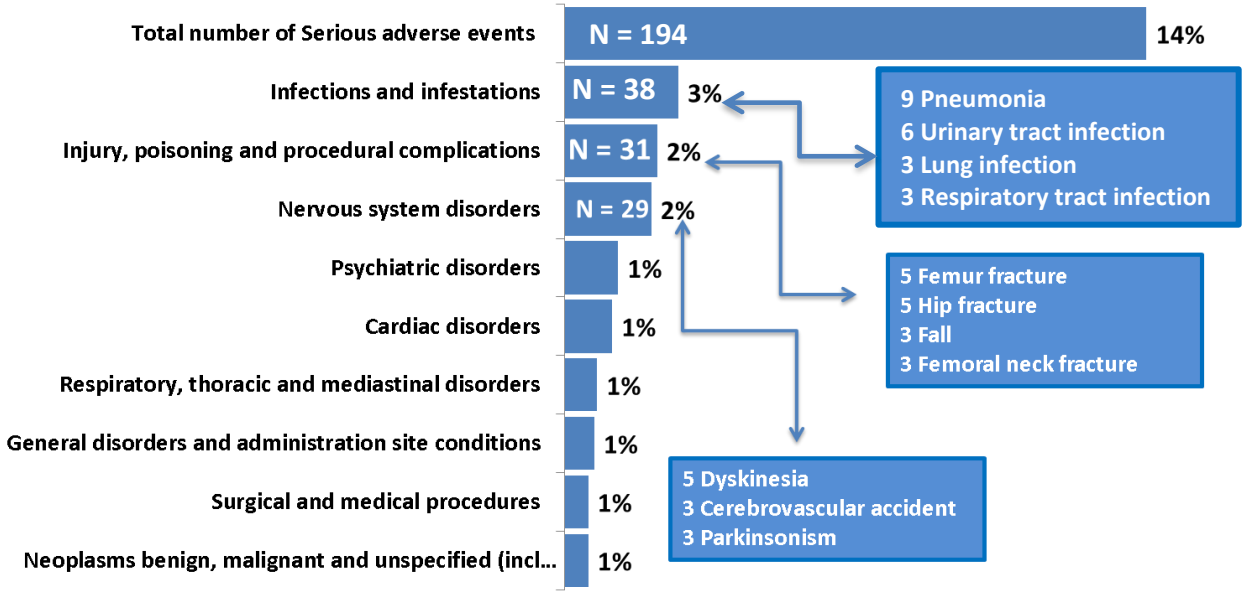
As for dyskinesia, 183 (11.7%) patients had at least one adverse event of dyskinesia (Total number of AE of dyskinesia N=197, 13.7%). Considering these 183 patients, 165 (12.5%) had safinamide appropriate use and 18 (7.7%) non-appropriate use. The total number of dyskinesia AEs was N=178 and N=19 in the group of patients with appropriate and non-appropriate use of safinamide, respectively.

10.4.1.2. Serious adverse events

As previously reported in paragraph 10.4.1.1., 194 serious adverse events occurred during the study in 143 (9.2% of evaluable patients) patients. SAE were 13.5% of all AEs. Seriousness criteria for 148 (10.3%) SAEs were new/prolonged hospitalization(s), for 24 (1.7%) were fatal, for 14 (1.0%) were other important medical events, for five (0.3%) they resulted in persistent/significant disability/incapacity and for three (0.2%) they were life threatening.
The most frequently reported SAEs were in the Infections and infestations (N=38, 2.6% of all occurred AEs), Injury, poisoning and procedural complications (N=31, 2.2%) and Nervous system disorders (N=29, 2.0%) SOC. In **Figure 10.4.1.2: 1** SAEs with frequency ≥0.5% are described according to SOC.
Among the 38 Infections and Infestations AEs, the following were the most frequently reported: pneumonia (N=9), urinary tract infections (N=6), lung infections (N=3) and respiratory tract infections (N=3); while, as showed in **Figure 10.4.1.2: 1,** among the 31 Injury, poisoning and procedural complications AEs, the following were the most frequently reported: femur fractures (N=5), hip fractures (N=5), falls (N=3) and femoral neck fractures (N=3). Among the 29

Nervous system disorders AEs there were five dyskinesias, three cerebrovascular accidents and three parkinsonisms. The detailed distribution of all serious adverse events by SOC and PT is shown in Table 34 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).

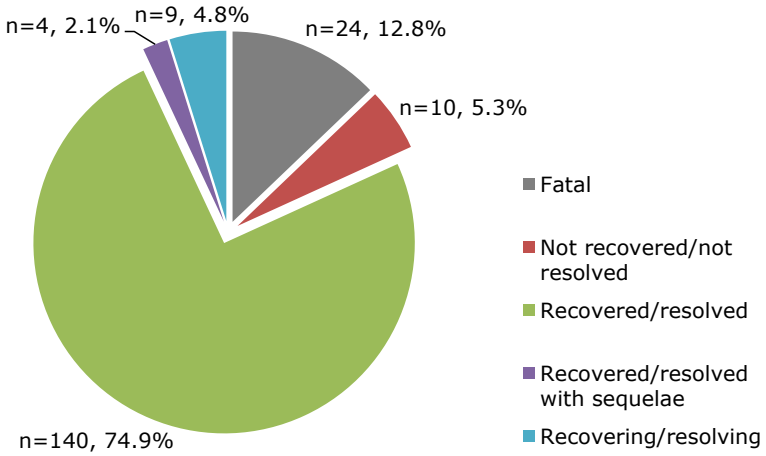
Figure 10.4.1.2: 1 Serious adverse events: System Organ Class



Note. Classes with frequency <0.5% are not shown.

The outcome of the SAE was available for 187/194 events; the **Figure 10.4.1.2: 2** shows the distribution of SAEs according to outcome; 24 SAEs (12.8%) had a fatal outcome.

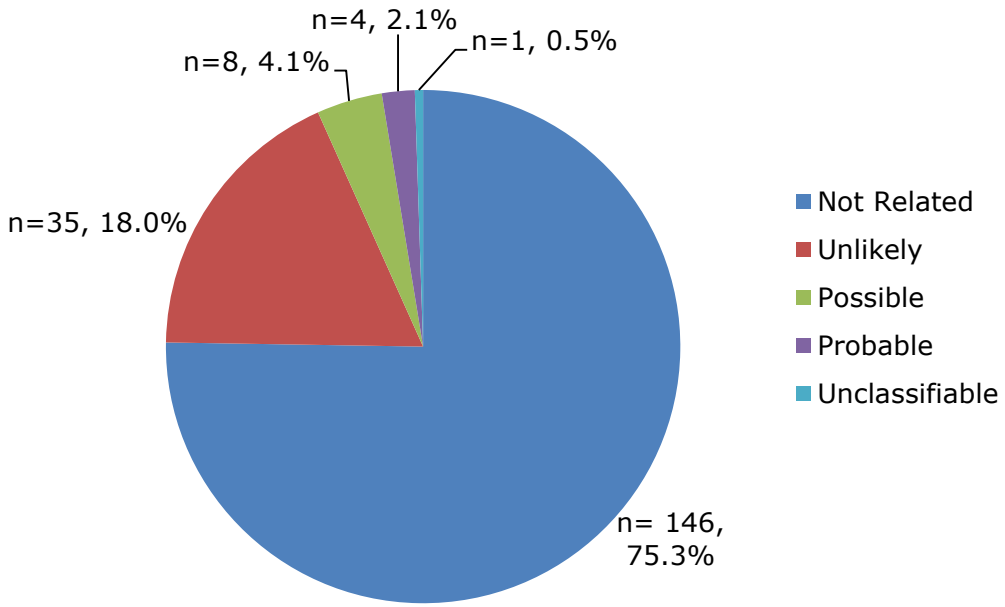
Figure 10.4.1.2: 2 Serious adverse events: outcome



Note. Percentages were computed out of the total number of occurred SAEs. 7 SAEs had unknown outcome

The detailed distribution of serious adverse events by outcome is shown in Table 37 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).
As outlined in **Figure 10.4.1.2: 3,** eight SAEs (4.1% of all SAEs) and four (2.1%) SAEs had a possible and probable relation with safinamide respectively. The figure shows the distribution of SAEs according to relation with drug under study. No SAEs had definite relation with safinamide. In Table 39 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report) the complete distribution of serious adverse events in relation to safinamide is reported. The most frequent events with probable relation with safinamide were three dyskinesias (+1 with possible relation) and one visual hallucination. Other events with possible relation were: one joint dislocation, one cognitive disorder, one epilepsy event, one agitation, one anxiety, one hallucination and one case of hypertension.

Figure 10.4.1.2: 3 Serious adverse events: relation with safinamide

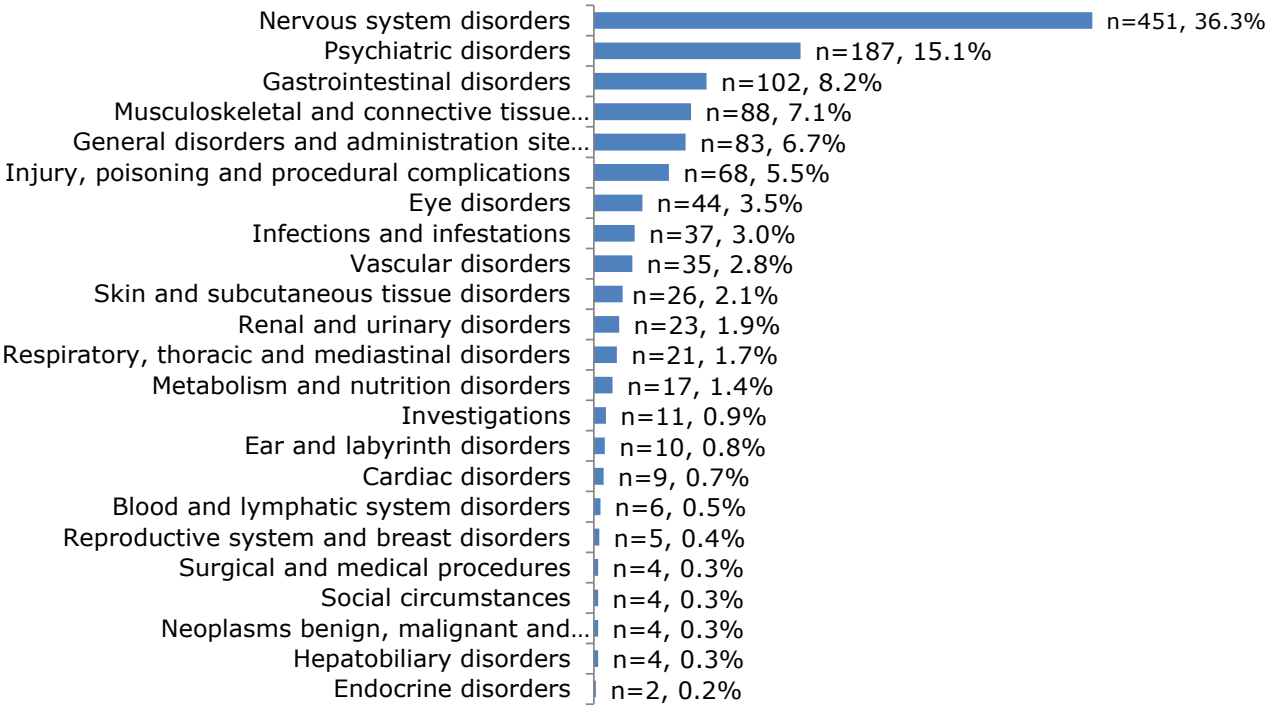


Note. Percentages were computed out of the total number of occurred SAEs.
For 156 SAEs (10.9%) no action was taken, instead drug was permanently interrupted for 27 (1.9%) adverse events, the dosage was reduced in two (0.1%) events and the drug was temporarily interrupted in 5 (0.3%) events.
The distribution of occurred serious adverse events by action taken in the overall sample is shown in Table 41 of the Final Statistical Report (**see Attachment 6**); in the table events are classified by SOC and PT.

10.4.1.3. Non-serious adverse events

Out of the 1435 adverse events during the study, 1241 (86.5%) were non serious.
The most frequently reported adverse events belonged to the Nervous system disorders (N=451, 36.3% of all occurred non serious AEs) and the Psychiatric disorders SOC (N=187, 15.1%).
In **Figure 10.4.1.3: 1** all non-serious AEs are presented according to SOC.
Among the 451 nervous system disorders, the most frequently reported were dyskinesia (N=192) and dizziness (N=39), while among 187 psychiatric disorders, the most frequent were: hallucination (N=39) and anxiety (N=19). Among 102 gastrointestinal disorders nausea was the most frequent (N=22).
The detailed distribution of all non-serious adverse events by SOC and PT is shown in Table 33 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).

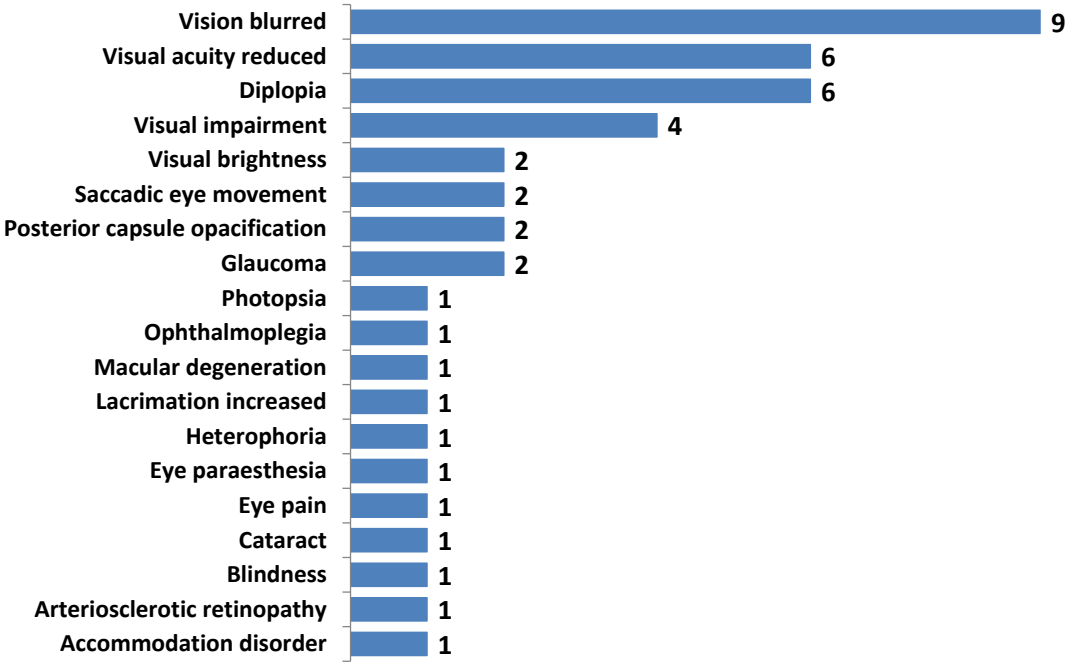
Figure 10.4.1.3: 1 Non-serious adverse events: System Organ Class



Note. Percentages were computed out of the total number of occurred non serious adverse events.

Fourty-four adverse events (3.5%) belonged to the Eye disorders class; the distribution of these events is shown in **Figure 10.4.1.3:2**.

Figure 10.4.1.3: 2 Non-serious adverse events: Eye disorders



10.4.1.4. Special Safety Situations

In total 14 (1.0%) special safety situations occurred in 10 patients. In six cases there was a suspected drug-drug interaction, in four cases a lack of efficacy, and in one both suspected drug interaction and lack of efficacy; one episode of medication error of safinamide, one episode of occupational exposure to safinamide and one episode of off-label use of safinamide occurred too.
The listing of adverse events related to a special safety situation is shown in Table 43 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).

As declared by investigators, 94 (6.8%), 68 (5.1%) and 42 (3.2%) patients had at least one special safety situation at 4-month, 8-month and 12-month follow up respectively. In **Table 10.4.1.4: 1** the detail of these special situations is shown.

Table 10.4.1.4: 1 Special safety situations during observation as declared by investigator

	Total evaluable patients at 4-month (N= 1373)	Total evaluable patients at 8-month (N= 1323)	Total evaluable patients at 12-month (N= 1326)
Patients with at least one special safety situation at follow-up	94 (6.8%)	68 (5.1%)	42 (3.2%)
Overdose	2 (2.1%)	0 (0%)	1 (2.4%)
Misuse	3 (3.2%)	1 (1.5%)	0 (0%)
Lack of efficacy	35 (37.2%)	19 (27.9%)	13 (31.0%)
Suspected drug interaction with safinamide	6 (6.4%)	1 (1.5%)	1 (2.4%)
Episode of off-label use of safinamide	57 (60.6%)	50 (73.5%)	27 (64.3%)
Episode of medication error of safinamide	1 (1.1%)	0 (0%)	0 (0%)

Note. Percentages of patients with at least one special safety situation at follow-up are computed out of the total number of of patients evaluable for FAS and 4-, 8- or 12-month follow up.
Note. Percentages of special safety situatiotions are computed out of the total number of patients evaluable for FAS and 4-, 8- or 12-month follow-up with at least one special safety situation. A patient could have more than one special safety situation.

10.4.1.5. Safinamide non-appropriate use

A total of 233 (16.9%) evaluable patients had non appropriate use of safinamide. German patients were excluded from this evaluation because of selection criteria defined by amended protocol. As shown in **Table 10.4.1.5: 1** the primary reasons of inappropriate use was the absence of fluctuation at the start of treatment of safinamide (N=121, 8.8%) and safinamide starting dosage different from 50 mg/die (N=105, 7.6%). In 21 patients safinamide was administered without concomitant levodopa (in these patients Dopamine agonist was the most frequent concomitant treatment), and it was administered to 16 patients without idiopathic Parkinson's disease diagnosis. Finally for 11 patients a concomitant treatment with MAO inhibitors was recorded when the safinamide treatment was started.

Table 10.4.1.5: 1 Safinamide non-appropriate use at treatment start (overall)

Non-appropriate use	N	%
Any	233	16.9%
Patients without fluctuation at the start of treatment of safinamide	121	8.8%
Patients that start safinamide with a dosage different from 50 mg/die	105	7.6%
Patients without levodopa in addition to safinamide	21	1.5%
Patients with PD different from Idiopatic PD	16	1.2%
Patients in concomitant treatment with other monoamine oxidase (MAO) inhibitors	11	0.8%

Note. Percentages were computed out of the number of evaluable patients for FAS, excluding German patients (N=1377).
Note. Data sorted by descending frequency of non-appropriate use.
PD: Parkinsons' disease.

The SYNAPSES study is a drug-utilization study, therefore the real practice was observed and data about inappropriate use of safinamide were captured. Although not initially foreseen by the study protocol, a descriptive analysis on the frequency of safety events was provided in patients undergoing appropriate use of safinamide vs inappropriate use. In **Table 10.4.1.5: 2** the frequency of patients with at least one AE, SAE, ADR and SADR separately in patients with inappropriate and appropriate use of safinamide are shown, together with the total number of observed events.

Table 10.4.1.5: 2 Adverse events and safinamide: appropriate and non-appropriate use during observation (overall)

	Non appropriate use (N= 233)	Appropriate use (N= 1325)	FAS (N= 1558)
Patients with at least one AE (N, %)	116 (49.8%)	598 (45.1%)	714 (45.8%)
Patients with at least one SAE (N, %)	17 (7.3%)	126 (9.5%)	143 (9.2%)
Patients with at least one ADR (N, %)	56 (24.0%)	376 (28.4%)	432 (27.7%)
Patients with at least one SADR (N, %)	2 (0.9%)	34 (2.6%)	36 (2.3%)
Total number of AEs (N)	194	1241	1435
Total number of SAEs (N)	20	174	194
Total number of ADRs (N)	80	605	685
Total number of SADRs (N)	2	46	48

Note. Percentages are computed out of the total number of patients evaluable at enrolment by use of safinamide
AE: Adverse Event. ADR: Adverse Drug Reaction. SADR: Serious Adverse Drug Reaction. SAE: Serious Adverse Event.

At follow up, 38 (2.8%), 33 (2.5%) and 17 (1.3%) patients had inappropriate use at 4-month, 8-month and 12-month follow up respectively, mainly due to the fact that at least one dosage of safinamide not concomitant with levodopa was administered (1.8% of patients at 4-month and 8-month follow up and 1.3% at 12-month follow up) (see **Table 10.4.1.5: 3** for further details).

Table 10.4.1.5: 3 Adverse events and safinamide: non-appropriate use during observation (overall)

	4-month follow up		8-month follow up		12-month follow up	
	N, %	95% CI	N, %	95% CI	N, %	95% CI
Any inappropriate use during follow-up	38 (2.77%)	1.97-3.78	33 (2.49%)	1.72-3.49	17 (1.28%)	0.75-2.04
At least one dosage of safinamide not concomitant with Levodopa	25 (1.82%)	1.18-2.68	24 (1.81%)	1.17-2.69	17 (1.28%)	0.75-2.04
Patients in concomitant treatment with other monoamine oxidase (MAO) inhibitors	13 (0.95%)	0.51-1.61	9 (0.68%)	0.31-1.29	-	-

Note. Percentages of 4-month follow-up were computed out of the number of evaluable patients for the full analysis set at enrollment and at 4-month follow-up (N=1373); percentages of 8-month follow up were computed out of the number of evaluable patients for the full analysis set at enrolment and at 8-month follow-up (N=1323); percentages of 12-month follow up were computed out of the number of evaluable patients for the full analysis set at enrolment and at 12-month follow-up (N=1326).

10.4.2 Secondary Endpoint(s)/Outcome(s)

10.4.2.1 Secondary Objective #1: Description of patients treated with safinamide according to clinical practice

Characteristics of patients treated with safinamide according to clinical practice (demographics, disease duration, disease severity, concomitant relevant conditions with particular focus on psychiatric ones) were previously described in paragraph 10.2.

Moreover, evaluable patients were previously described in paragraph 10.2.7 according to treatments for PD terminated before starting the safinamide treatment, and in paragraph 10.4.2.2.2 according to ongoing treatments for PD at the start of safinamide treatment; also any concomitant use of psychiatric therapies at the start of treatment with safinamide is described in paragraph 10.4.2.2.3

10.4.2.2 Secondary Objective #2: Description of safinamide treatment patterns in real-life setting

10.4.2.2.1. Treatment with safinamide (overall)

At the start of treatment with safinamide, the majority of patients (N=1452, 93.2%) were administered a daily dose of one tablet (50 mg); 94 patients (6.0%) were administered with one 100 mg tablet, 7 patients (0.4%) with ½ tablet (i.e. 25 mg daily), 2 patients (0.1%) with 1/4 tablet (i.e. 12.5 mg daily), 2 patients (0.1%) two tablets (i.e. 100 mg daily) and 1 patient (0.1%) with ½ 100 mg tablet (i.e. 50 mg daily).

During the observation period, 904 patients (58.0%) had a dose increase of safinamide and 98 (6.3%) had a dose decrease.

Safinamide temporary discontinuation was observed for 68 patients (4.4%).

During the study, 336 (21.6%) of evaluable patients permanently discontinued safinamide. Main reasons for discontinuation were: adverse reaction (N=161, 47.9%), patient choice (N=81,

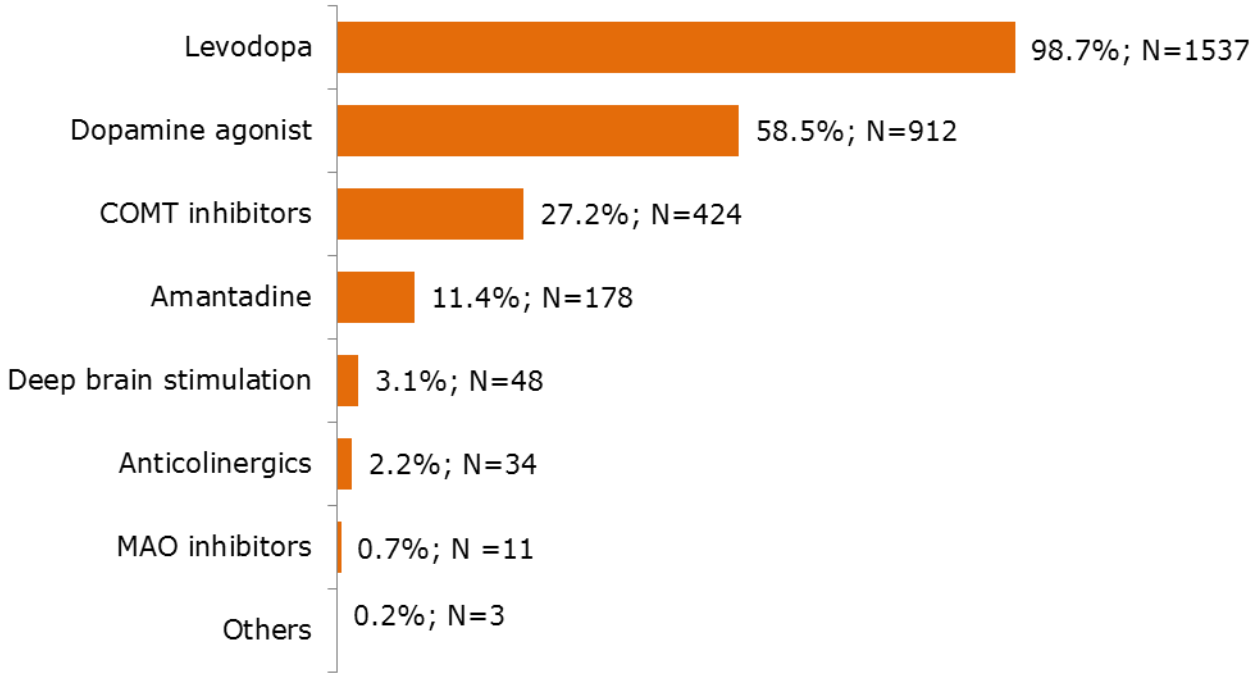
24.1%), disease progression (N=20, 6.0%) and other reasons (N=74, 22.0%, among which were lack of efficacy (N=13), medical decision (N=10), deep brain stimulation (N=10), adverse events (N=8), death (N=7), no clinical improvement (N=5), etc,…).

10.4.2.2.2. Treatments concomitant to safinamide: PD treatments at the start of safinamide (overall)

Almost all patients (N=1556, 99.9%) had one ongoing treatment for PD at the start of safinamide therapy. As shown in **Figure 10.4.2.2.2: 1**, during treatment with safinamide, 98.7% (N=1537) of patients assumed levodopa, 58.5% (N=912) dopamine agonist, 27.2% (N=424) COMT inhibitors and 11.4% (N=178) amantadine.

The complete distribution of PD treatments by category and active is reported in **Table 10.4.2.2.2: 1.**

Figure 10.4.2.2.2: 1 PD treatments concomitant to safinamide (overall)



Note. Percentages were computed out of the total number of patients evaluable for the FAS (N=1558).

Table 10.4.2.2.2: 1 PD treatments ongoing at the start of safinamide (overall)

Categories	Active	FAS (N= 1558)
≥ 1 ongoing PD treatment	**Any**	**1556 (99.9%)**
Amantadine	**Any**	**178 (11.4%)**
	Amantadine	78 (5.0%)
	Amantadine hydrochloride	86 (5.5%)
	Amantadine sulfate	14 (0.9%)
Anticolinergics	**Any**	**34 (2.2%)**
	Biperiden	10 (0.6%)
	Bornaprine hydrochloride	3 (0.2%)
	Orphenadrine	1 (0.1%)
	Procyclidine hydrochloride	1 (0.1%)
	Trihexyphenidyl	2 (0.1%)
	Trihexyphenidyl hydrochloride	17 (1.1%)
COMT inhibitors	**Any**	**424 (27.2%)**
	Carbidopa - Entacapone - Levodopa	331 (21.2%)
	Carbidopa Monohydrate - Entacapone - Levodopa	2 (0.1%)
	Entacapone	29 (1.9%)

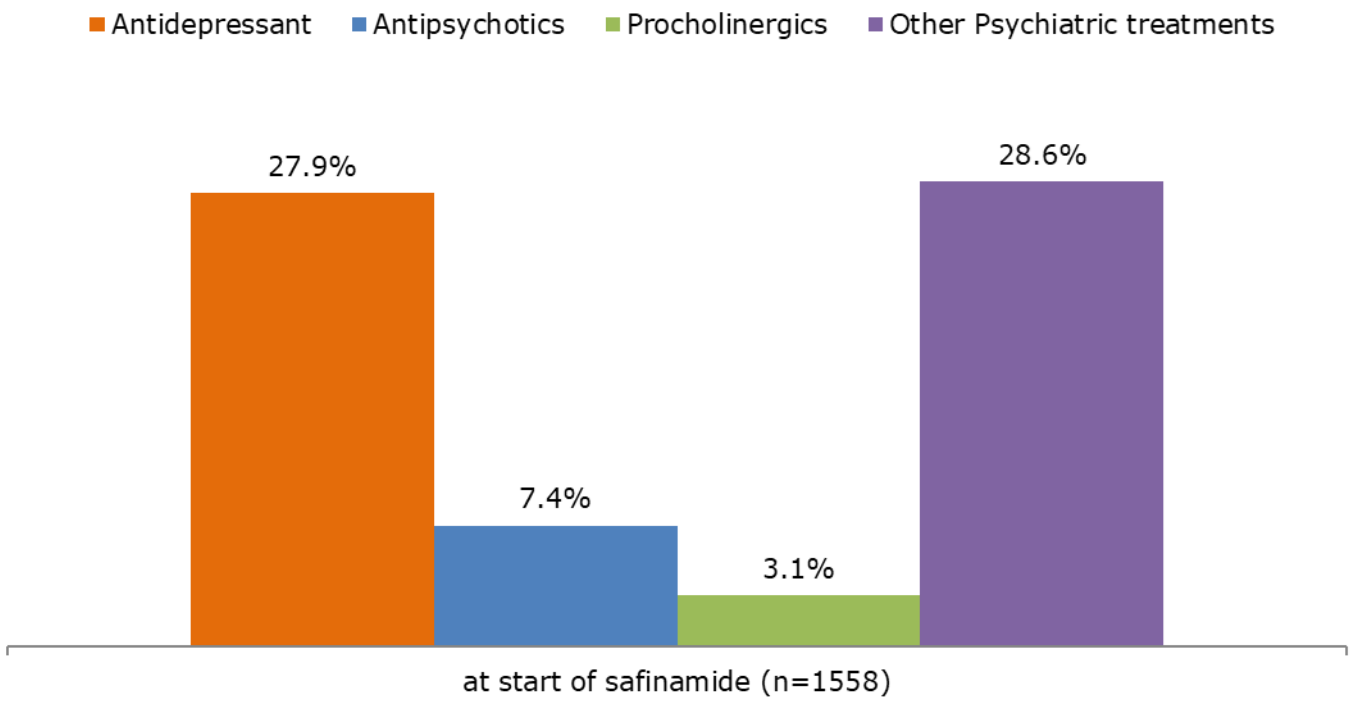
Categories	Active	FAS (N= 1558)
	Opicapone	43 (2.8%)
	Tolcapone	21 (1.3%)
Dopamine agonists	**Any**	**912 (58.5%)**
	Apomorphine hydrochloride	17 (1.1%)
	Bromocriptine	1 (0.1%)
	Cabergoline	1 (0.1%)
	Pergolide mesilate	1 (0.1%)
	Piribedil	5 (0.3%)
	Pramipexole	94 (6.0%)
	Pramipexole dihydrochloride	335 (21.5%)
	Ropinirole hydrochloride	234 (15.0%)
	Rotigotine	252 (16.2%)
Levodopa	**Any**	**1537 (98.7%)**
	Benserazide hydrochloride - Levodopa	655 (42.0%)
	Carbidopa - Levodopa	574 (36.8%)
	Carbidopa - Melevodopa	142 (9.1%)
	Carbidopa - Entacapone - Levodopa	331 (21.2%)
	Carbidopa Monohydrate - Levodopa	193 (12.4%)
	Carbidopa Monohydrate - Entacapone - Levodopa	2 (0.1%)
	Levodopa	16 (1.0%)
MAO inhibitors	**Any**	**11 (0.7%)**
	Rasagiline	5 (0.3%)
	Rasagiline mesylate	6 (0.4%)
Medical device to treat PD	**Any**	**48 (3.1%)**
	DEEP BRAIN STIMULATION	48 (3.1%)
Others	**Any**	**3 (0.2%)**
	Botulinum toxin type a	3 (0.2%)

Note. Percentages were computed out of the total number of patients evaluable for the FAS. A patient could have had more than one previous and terminated PD treatment.
Note. Carbidopa-Entacapone-Levodopa is shown both as Levodopa and as COMT inhibitors

10.4.2.2.3. Treatments concomitant to safinamide: psychiatric treatments during observation (overall)

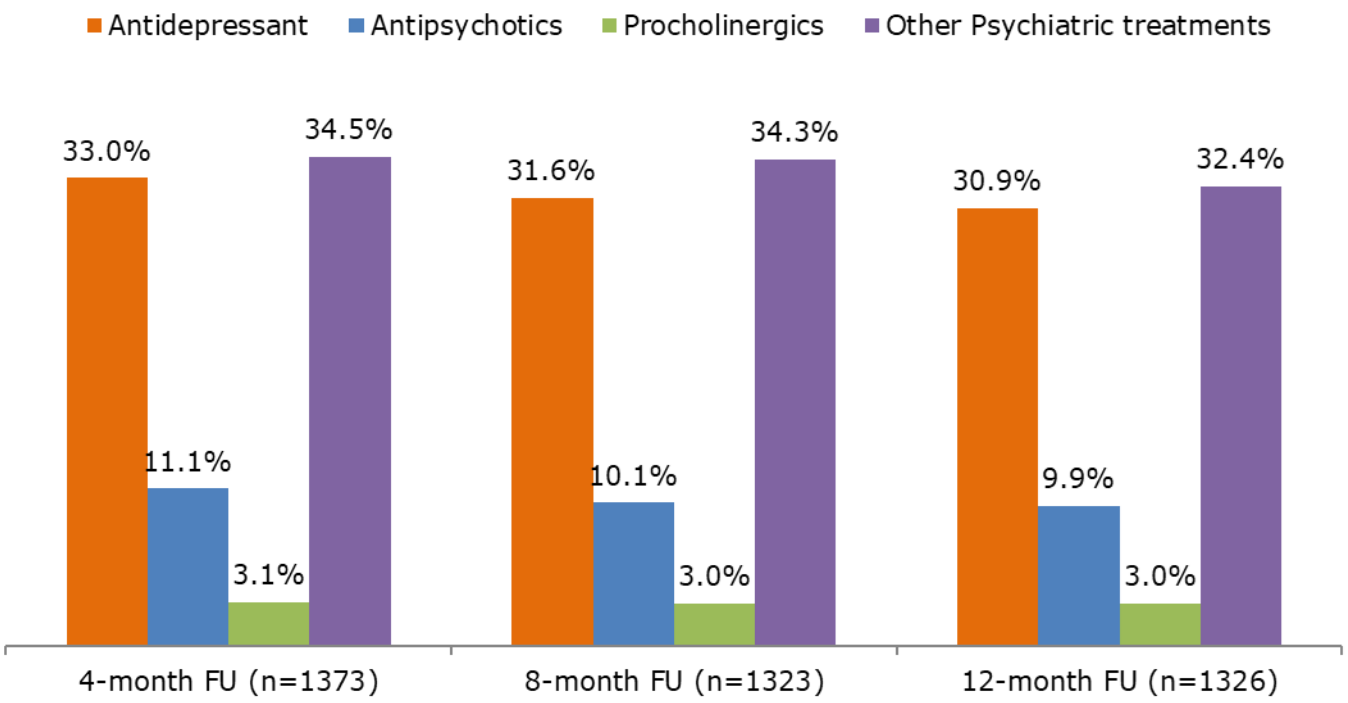
The distribution of patients according to psychiatric treatments at start of safinamide is shown in **Figure 10.4.2.2.3: 1:** 435 (27.9%) patients assumed antidepressants, 115 (7.4%) antipsychotics and 48 (3.1%) procholinergics, while other psychiatric treatments were given to 446 (28.6%) patients.
The distribution of patients according to psychiatric treatments during the study is shown in **Figure 10.4.2.2.3: 2**: while procholinergics use remains stable during the study at around 3.0%, the use of antidepressants (N=453, 33.0% N=418, 31.6% and N=410, 30.9% at 4-month, 8-month and 12-month follow up respectively), antipsychotics (N=152, 11.1% N=133, 10.1% and N=131, 9.9% at 4-month, 8-month and 12-month follow up respectively) and other psychiatric therapies (N=474, 34.5% N=454, 34.3% and N=430, 32.4% at 4-month, 8-month and 12-month follow up respectively) increased at follow up visits compared to the start of safinamide treatment.

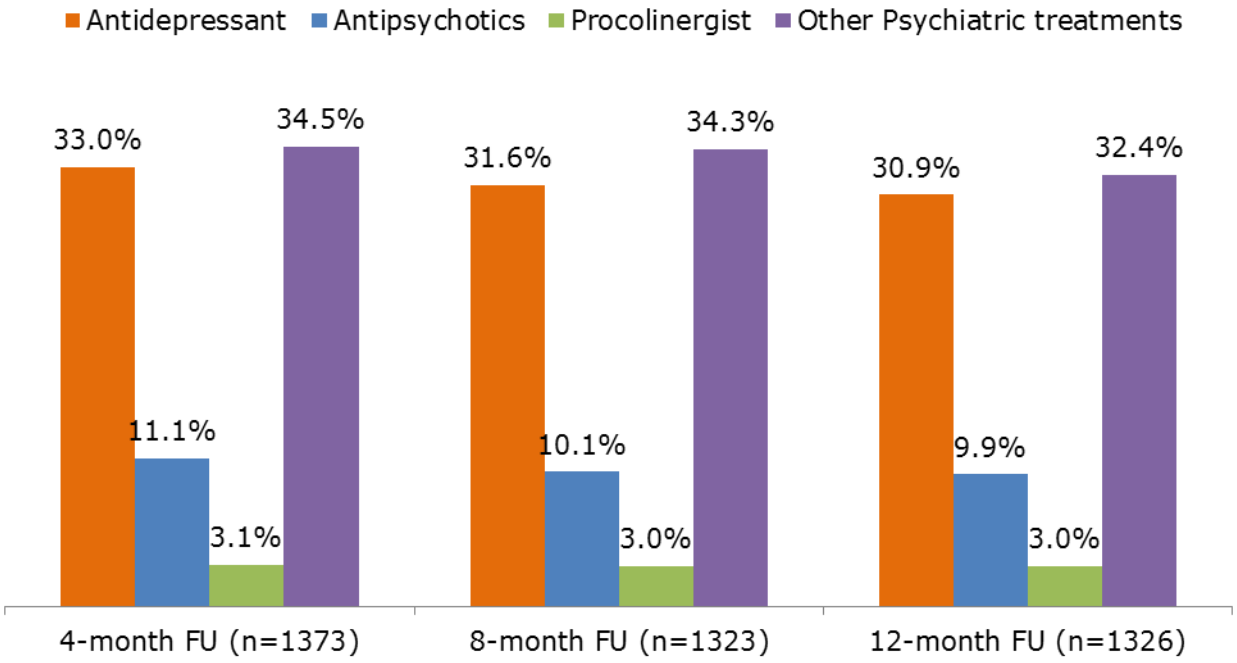
Figure 10.4.2.2.3: 1 Psychiatric treatments concomitant to safinamide at start of safinamide (overall)



Note. Percentages were computed out of the total number of patients evaluable for the FAS. A patient could have more than one concomitant use of psychiatric therapy.

Figure 10.4.2.2.3: 2 Psychiatric treatments concomitant to safinamide during the study (overall)



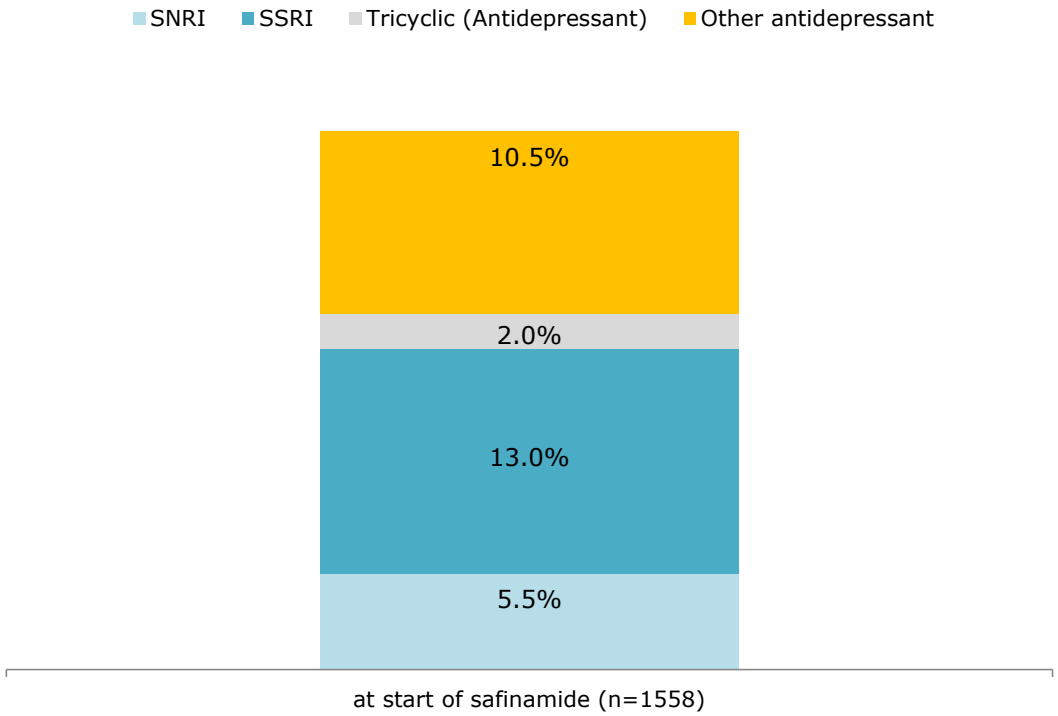


Note. Percentages were computed out of the total number of patients evaluable for the FAS and evaluable at each follow up visit. The same patient could have more than one concomitant use of psychiatric therapy.

Figure 10.4.2.2.3: 3 shows the distribution of patients according to antidepressant therapies at start of safinamide: 203 (13.0%), 164 (10.5%), 86 (5.5%) and 31 (2.0%) patients took SSRI, other antidepressants, SNRI and tricyclic respectively.

Figure 10.4.2.2.3: 3 Antidepressants treatments at start of safinamide treatment

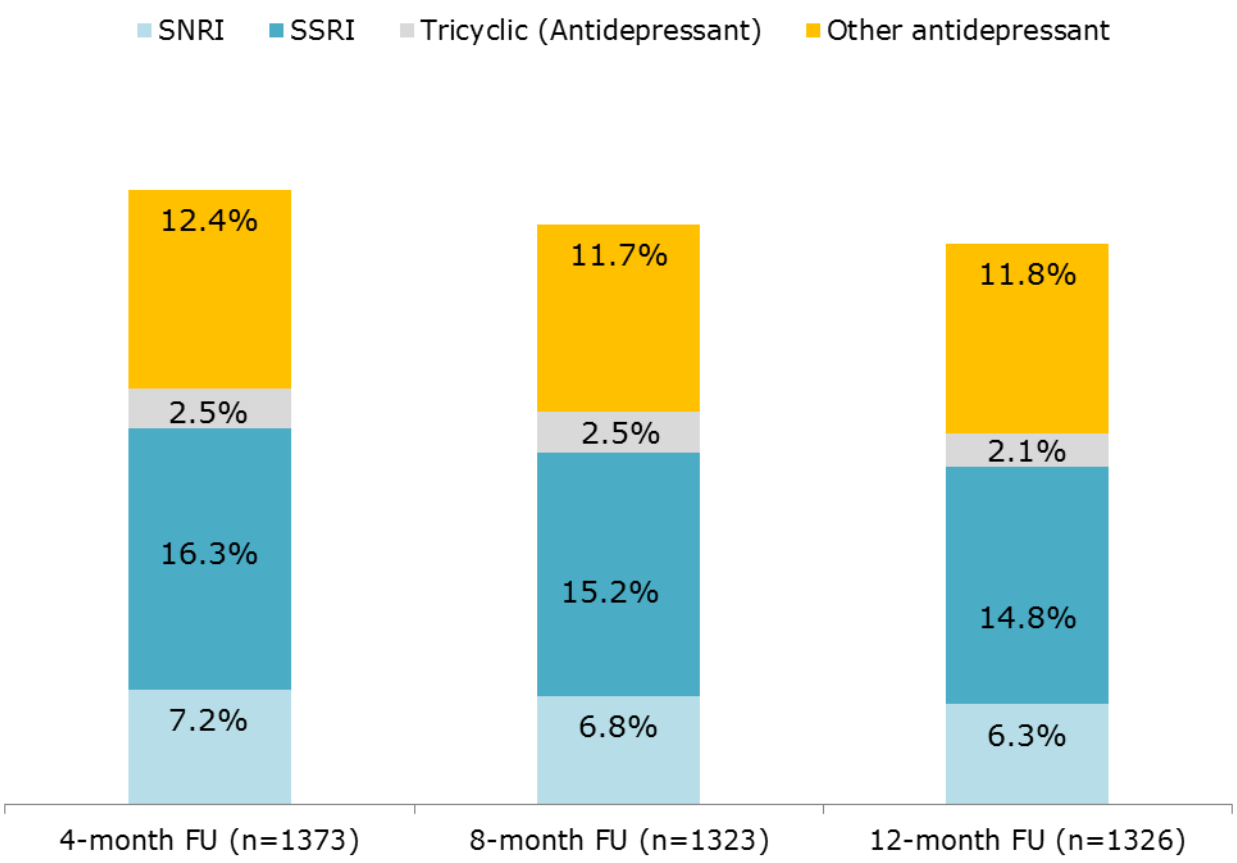
(overall)



Note. Percentages were computed out of the total number of patients evaluable for the FAS. The same patient could have more than one concomitant use of psychiatric therapy.

Figure 10.4.2.2.3: 4 shows the distribution of patients according to antidepressant therapies during the study: at all study visits the SSRI were the most frequently assumed antidepressant (13.0% (N=203), 16.3% (N=224), 15.2% (N=201) and 14.8% (N=196) at start of safinamide, 4-month, 8-month and 12-month follow up, respectively).

Figure 10.4.2.2.3: 4 Antidepressants treatments concomitant to safinamide during study (overall)


SNRI
SSRI
Tricyclic (Antidepressant)
Other antidepressant
12.4%
2.5%
16.3%
7.2%
11.7%
2.5%
15.2%
6.8%
11.8%
2.1%
14.8%
6.3%
4-month FU (n=1373)
8-month FU (n=1323)
12-month FU (n=1326)

Note. Percentages were computed out of the total number of patients evaluable for the FAS and evaluable at each follow up visit. The same patient could have more than one concomitant use of psychiatric therapy.

10.4.2.2.4. Treatments concomitant to safinamide: treatments for any other medical condition (overall)

In Annex 2.1 (*Table A2 Treatments for any other medical condition received during observation*) the distribution of patients according to treatments for any other medical condition, received by the patients with safinamide, is shown.

10.5. Other analyses

In the following paragraphs results of analyses by subgroup of patients (patients aged >75, those with relevant comorbidities and those with relevant psychiatric conditions) are summarized.

10.5.1 Safety in Elderly Patients

10.5.1.1. Safinamide treatment patterns

No relevant differences emerged in safinamide initial daily dose by younger and older patients; at start of treatment, the majority of patients (N=1089, 93.3% in patients aged ≤75 and N=363, 92.8% in patients aged >75) received a daily dose of one tablet (50 mg).

One 100-mg tablet was administered as starting dose to 70 patients (6.0%) aged ≤75 and to 24 patients (6.1%) aged >75. Moreover, one patient (0.1%) aged ≤75 and one patient (0.3%) aged >75 received two 50mg-tablets as starting daily dose (i.e. 100 mg daily dose).

In the group of patients aged ≤75, four (0.3%), two (0.2%), one (0.1%) patients were administered 1/2 50-mg tablet (i.e. 25 mg daily dose), 1/450-mg tablet (i.e. 12.5 mg daily dose), ½ 100-mg tablet (i.e. 50 mg daily dose), respectively. In older patients, three (0.8%) patients were administered 1/2 50-mg tablet (25 mg daily dose) and two 50-mg tablets (100 mg daily dose), respectively.

During the observation period, in the group of patients aged ≤75, 690 patients (59.1%) had a dose increase of safinamide and 75 (6.4%) had a dose decrease, while 214 (54.7%) and 23 (5.9%) patients had a dose increase and a dose decrease, respectively, in the older patients.

Safinamide temporary discontinuation was observed for 53 (4.5%) and 15 (3.8%) patients aged ≤75 and >75 respectively.

During the study, 245 (21.0%) and 91 (23.3%) of evaluable patients aged ≤75 and >75 years respectively, permanently discontinued safinamide. The main reasons for discontinuation in patients aged ≤75 were: adverse reaction (N=117, 47.8%), patient choice (N=64, 26.1%), disease progression (N=13, 5.3%) and other reasons (N=51, 20.8%). In patients aged >75, the main reasons for discontinuation were: adverse reaction (N=44, 48.4%), patient choice (N=17, 18.7%), disease progression (N=7, 7.7%) and other reasons (N=23, 25.3%).

10.5.1.2. Adverse events

As shown in **Table 10.5.1.2:1**, during observation, 185 (47.3%) patients older than 75 had at least one AE (total number of AEs: 370) and 102 patients (26.1%) had at least one ADR (total number of ADRs: 155). Fifty-three (13.6%) patients had at least one SAE during observation and nine patients (2.3%)at least one SADR. The total number of SAEs and SADRs in this subpopulation were 74 and 11, respectively. It should be noted that, while the proportions of patients with at least one AE, ADR and SADR are similar in the population of patients aged >75 with respect to patients aged ≤75, the proportion of patients with ≥1 SAE is higher in patients aged >75 (N=53, 13.6%) with respect to patients aged ≤75 (N=90, 7.7%).

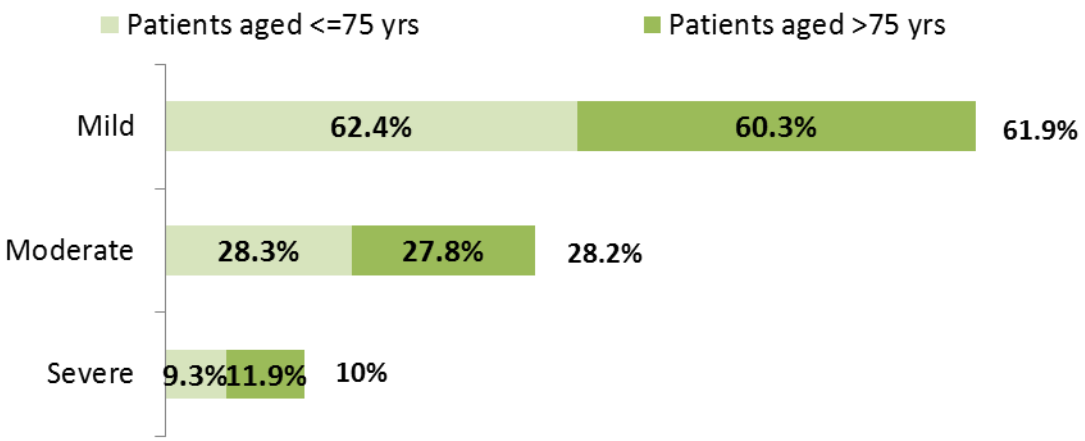
Table 10.5.1.2:1 Adverse events and adverse reactions during observation (overall)

	Pts aged ≤75 yrs (N= 1167)	**Pts aged >75 yrs (N= 391)**
Patients with at least one AE (N, %)	529 (45.3%)	185 (47.3%)
Patients with at least one SAE (N, %)	90 (7.7%)	53 (13.6%)
Patients with at least one ADR (N, %)	330 (28.3%)	102 (26.1%)
Patients with at least one SADR (N, %)	27 (2.3%)	9 (2.3%)
Total number of AEs (N)	1065	370
Total number of SAEs (N)	120	74
Total number of ADRs (N)	530	155
Total number of SADRs (N)	37	11

Note. Percentages are computed out of the total number of patients by age group.

Consistently with the previously reported results, with regard to severity, as shown in **Figure 10.5.1.2:1**, in older patients the frequency of severe events (N=44, 11.9%) is higher than in patients aged ≤75 (N=99, 9.3%).
The detailed distribution of adverse events severity by SOC and PT in patients aged ≤75 and >75 is shown in Table 35 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).

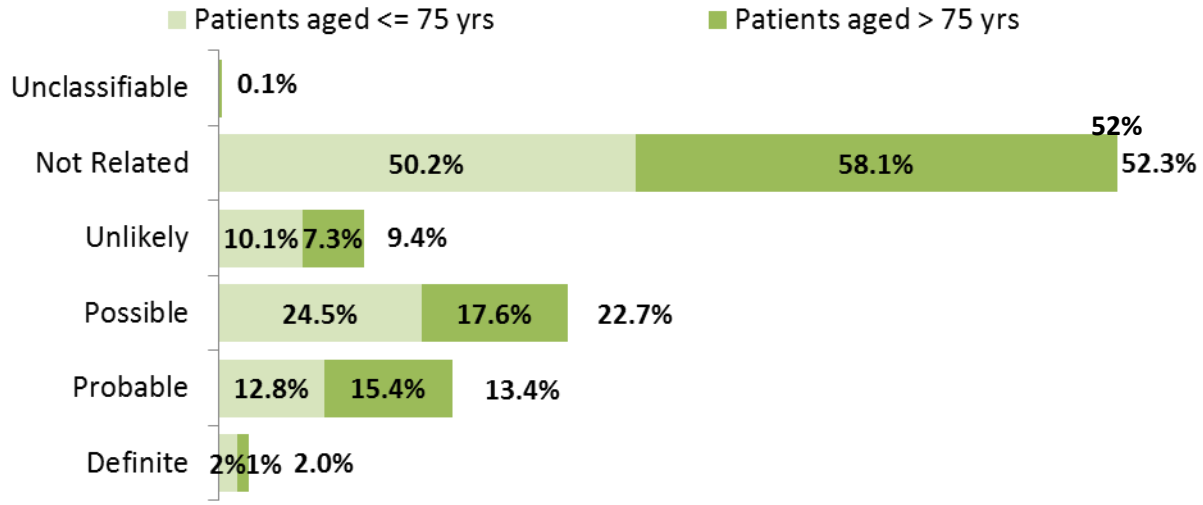
Figure 10.5.1.2:1 Adverse events severity (patients aged ≤75, >75)



Note. Percentages were computed out of the total number of AE by patient age.

Considering the total number of events in patients aged ≤75 (N=1065) and >75 (N=370), as shown in **Figure 10.5.1.2:2**, the proportion of events not related with safinamide was higher in patients aged >75 (N=215, 58.1% of the total events in this age group) than in patients aged ≤75 (N=535, 50.2%). In older patients, five (1.4%), 57 (15.4%) and 65 (17.6%) events had a definite, probable and possible relation with the drug under study, respectively.
Considering the events with definite relation with the drug under study, in patients aged >75 the following were reported: dizziness (N=1, 0.3%), dyskinesia (N=1, 0.3%), somnolence (N=1, 0.3%), agitation (N=1, 0.3%) and hallucination (N=1, 0.3%).

Figure 10.5.1.2: 2 Adverse events relation with safinamide (patients aged ≤75, >75)

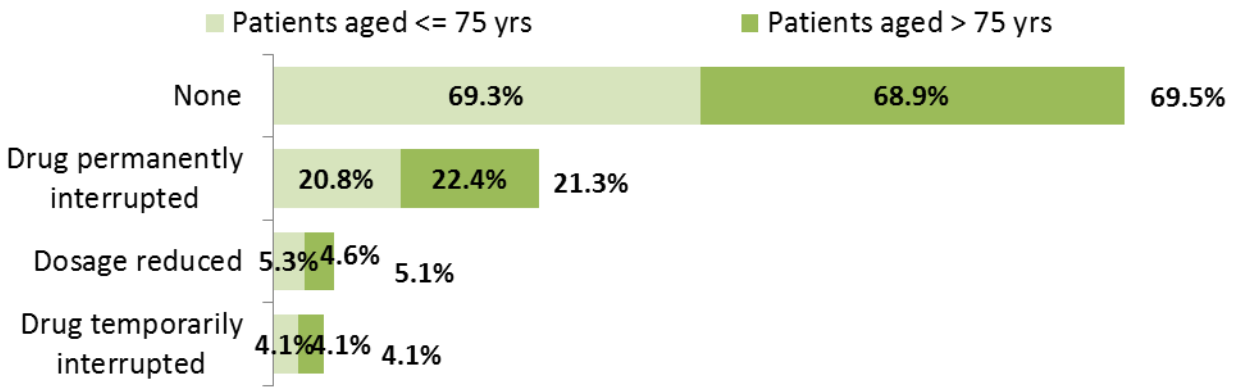


Note. Percentages were computed out of the total number of AE by patient age.

The distribution of occurred adverse events by causal relationship with safinamide in patients aged ≤75 and >75 is shown in Table 38 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report); in the table events are classified by SOC and PT.

Considering the 1065 and 370 adverse events in patients aged ≤ 75 and > 75 respectively, no relevant differences emerged in terms of action taken between the two age groups (as shown in **Figure 10.5.1.2: 3**). In older patients in 255 AEs (68.9%) no actions were taken; on the contrary, the drug was permanently interrupted in 83 (22.4%) adverse events, the dosage was reduced in 17 (4.6%) cases and the drug was temporarily interrupted in 15 (4.1%) cases.

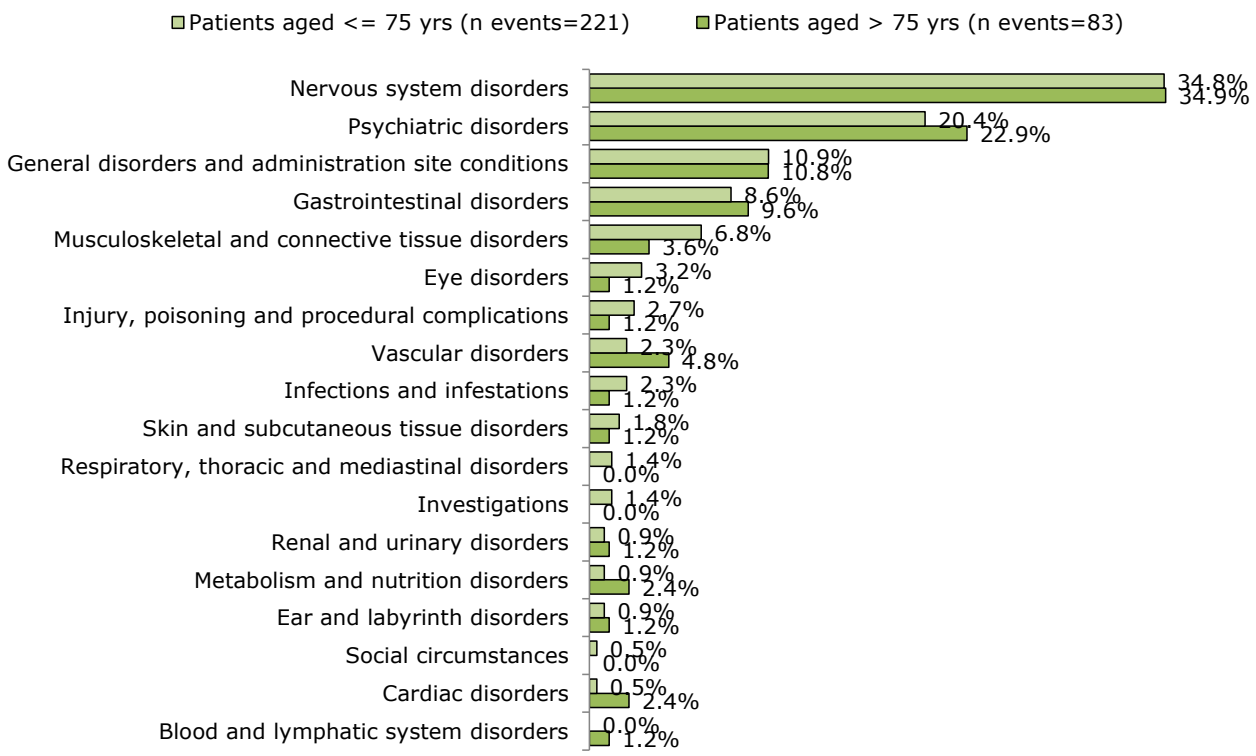
Figure 10.5.1.2: 3 Adverse events action taken (patients aged ≤75, >75)



Note. Percentages were computed out of the total number of AEs by patient age.

Figure 10.5.1.2: 4 shows the distribution of the 221 and 83 AEs causing safinamide permanent discontinuation in patients aged ≤ 75 and >75 respectively, by SOC. No relevant differences emerged in distribution between the two groups.

Figure 10.5.1.2: 4 Adverse events causing safinamide permanent discontinuation by System Organ Class (patients aged ≤75, >75)



Note. Percentages were computed out of the total number of AE causing safinamide permanent hdiscontinuation by patient age.

The distribution of occurred adverse events by action taken in patients aged ≤75 and >75 is shown in Table 40 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report); in the table events are classified by SOC and PT.

The outcome of the 1065 adverse events in patients aged ≤75 was as follows: recovered/resolved in 603 (56.6%) events, not recovered/not resolved in 256 (24.0%) events, recovering/resolving at the end of the observation in 109 (10.2%) events, fatal in 13 (1.2%) cases and recovered/resolved with sequelae in 6 (0.6%) cases.
Similar proportions were observed in the group of older patients being 221 (59.7%) the number of events recovered/resolved, whereas a slightly lower portion of events was not recovered/not resolved (N=74; 20.0%). A higher proportion of fatal events (N=11, 3.0%) and recovered/resolved with sequelae events (N=11, 3.0%) was observed in this age group compared to younger patients. Lastly, lower proportion of recovering/resolving events (N=23, 6.2%) was observed in this age group compared to younger patients.

As for dyskinesia, 149 (12.8%) and 34 (8.7%) patients, aged ≤75 and >75 respectively, had at least one adverse event of dyskinesia (Total number of AEs related to dyskinesia N=162 (15.2%) and 35 (9.5%) in patients aged ≤75 and >75 respectively).

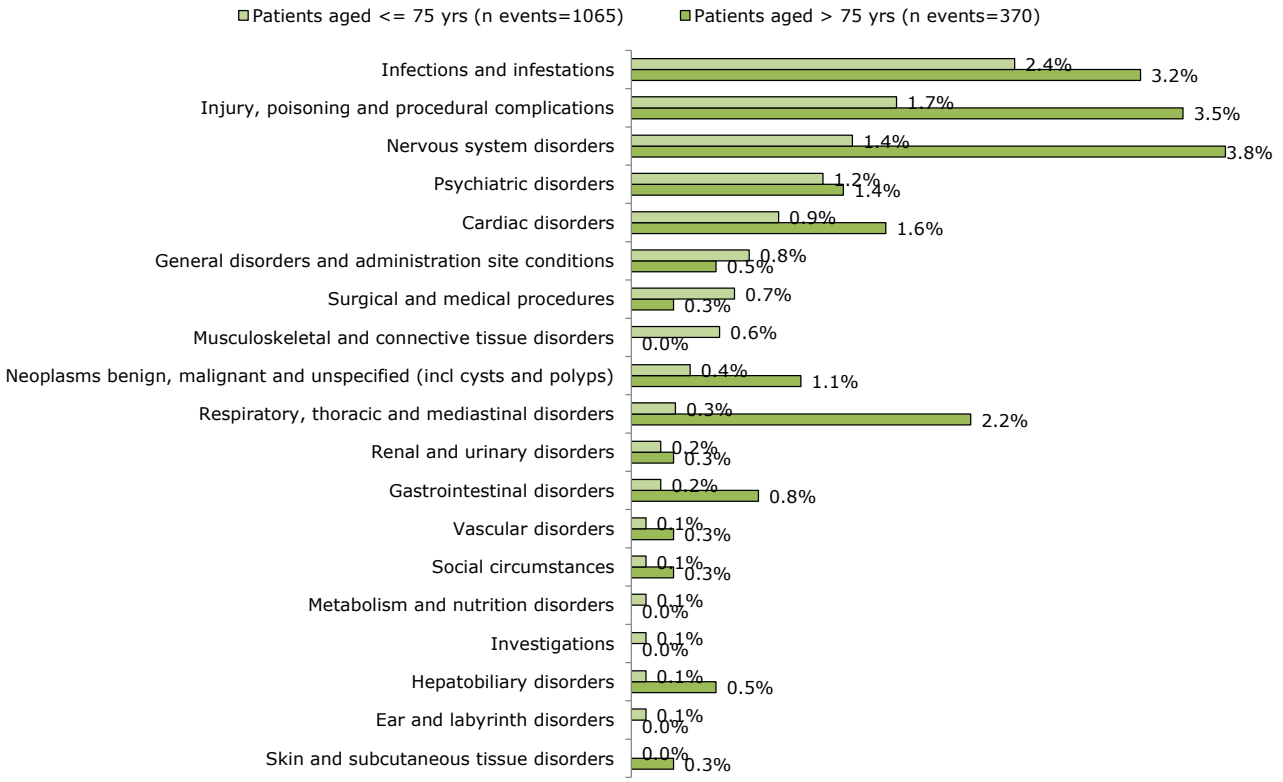
10.5.1.3. Serious adverse events

Patients aged ≤75 experienced 1065 adverse events, while patients aged >75 experienced 370 AEs; 120 (11.3%) and 74 (20.0%) events were serious in patients aged ≤75 and >75

respectively.
Seriousness criteria for SAEs occurred in patients aged ≤75 were new/prolonged hospitalization(s) in 92 (8.6%) cases, fatal in 13 (1.2%) cases, other important medical event(s) in nine (0.8%) cases, resulted in persistent/significant disability/incapacity in five (0.5%) cases and were life-threatening in one (0.1%) case.
Seriousness criteria for SAEs occurred in patients aged >75 were new/prolonged hospitalization(s) in 56 (15.1%) cases, fatal in 11 (3.0%) cases, other important medical event(s) in five (1.4%) cases and were life-threatening in two (0.5%) cases.

Out of the 194 SAEs, 61.9% (N=120) concerned patients aged ≤ 75 and 38.1% (N=74) patients aged > 75.
The most frequently reported (frequency ≥10%) SAEs in patients aged ≤ 75 years were SOC Infections and infestations (N=26, 2.4% of all AEs in this age group), Injury, poisoning and procedural complications (N=18, 1.7%), Nervous system disorders (N=15, 1.4%) and Psychiatric disorders (N=13, 1.2%), while the most frequently reported in patients aged > 75 were Nervous system disorders (N=14, 3.8% of all AEs in this age group), Injury, poisoning and procedural complications (N=13, 3.5%), Infections and infestations (N=12, 3.2%), Respiratory, thoracic and mediastinal disorders (N=8, 2.2%) SOCs.
In **Figure 10.5.1.3: 1** all SAEs are described according to SOC by age group.

Figure 10.5.1.3: 1 Serious adverse events: System Organ Class (patients aged ≤75, >75 yrs)



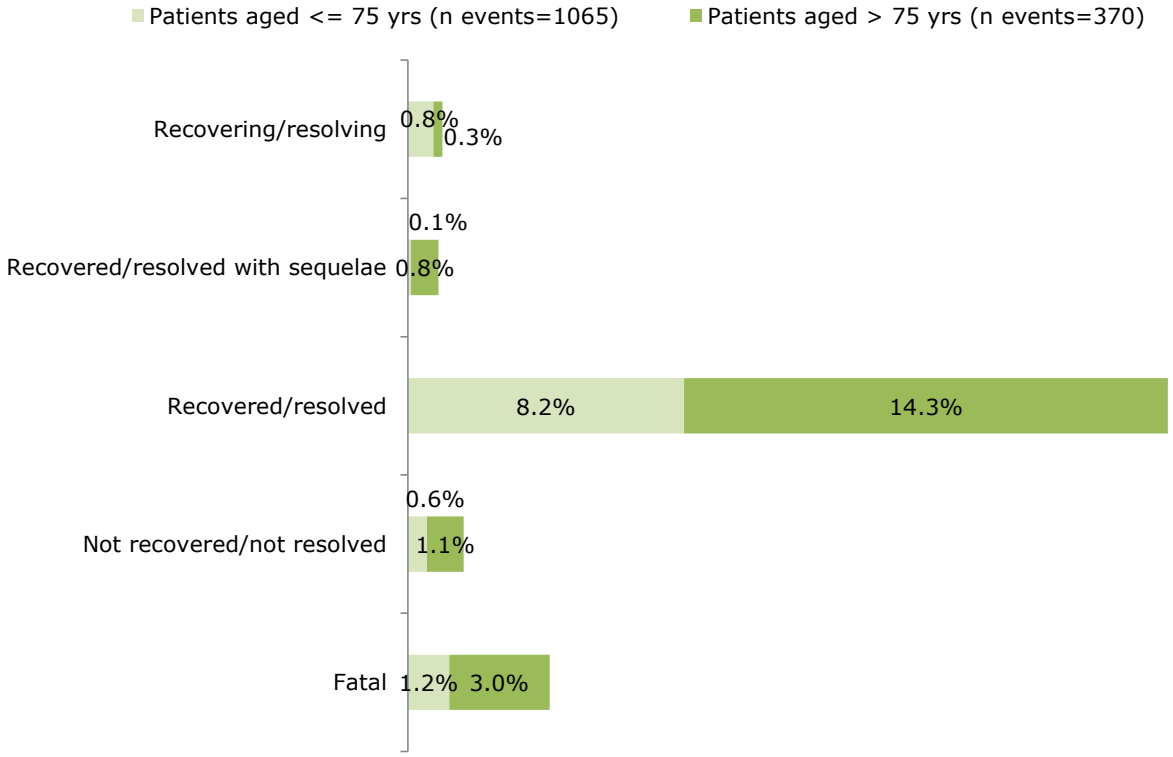
Note. Percentages were computed out of the total number of AEs by patient age.

In older patients, among the 14 SAEs in the Nervous system disorders SOC, the following events were reported: cerebrovascular accident (N=2), movement disorder (N=2), cerebral infarction (N=1), cerebrovascular disorder (N=1), cognitive disorder (N=1), dyskinesia (N=1), epilepsy (N=1), parkinsonism (N=1), presyncope (N=1), somnolence (N=1), subarachnoid haemorrhage

(N=1) and syncope (N=1).
SAEs mapping to Injury, poisoning and procedural complications SOC (N=13) in older patients were fractures (N=7: 3 hip, 2 upper limb 1 femur and 1 pelvic fracture), fall (N=2), brain contusion (N=1), head injury (N=1), limb injury (N=1) and skin injury (N=1).
The detailed distribution of all serious adverse events (by SOC and PT) in patients aged ≤75 and >75 is shown in Table 33 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).

Figure 10.5.1.3: 2 shows the distribution of SAEs according to outcome in the two groups; 13 SAEs (1.2% of all occurred SAEs in this age group) in patients aged ≤ 75 and 11 SAEs (3.0%) in patients aged > 75 had a fatal outcome. Similar portions of events resulted to be recovered between patients aged ≤ 75 and those aged > 75.

Figure 10.5.1.3: 2 Serious adverse events: outcome (patients aged ≤75, >75 yrs)

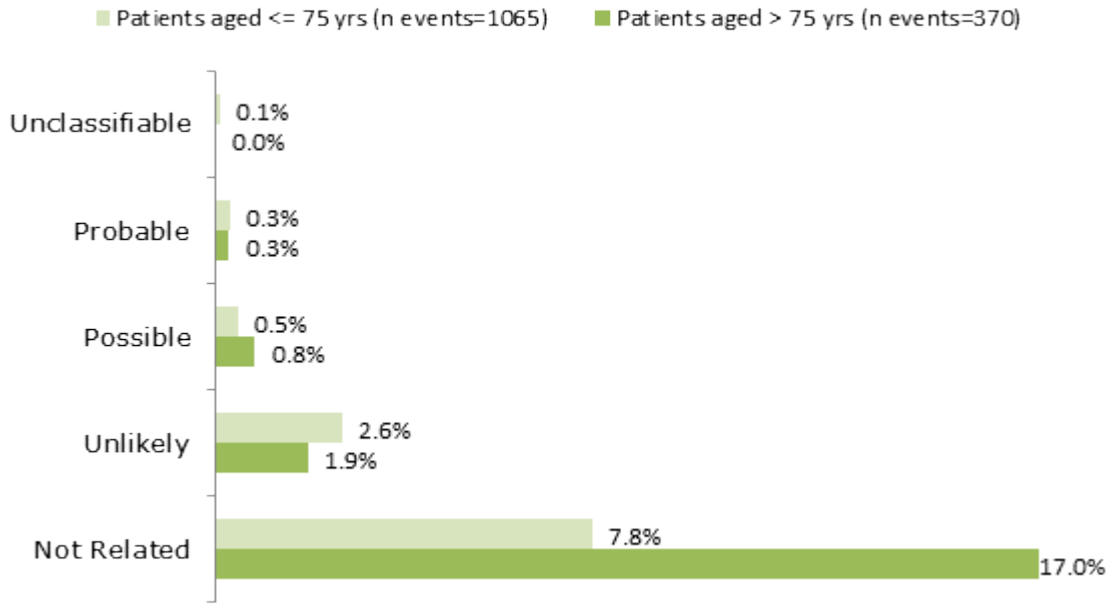


Note. Percentages were computed out of the total number of AEs by patient age.

The detailed distribution of serious adverse events by outcome in patients aged ≤75 and >75 years is shown in Table 37 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).

As outlined in **Figure 10.5.1.3: 3,** in the group of patients aged ≤75, five (0.5% of all AEs in this age group) and three (0.3%) SAEs had a possible and probable relation with safinamide, respectively. In the group of patients aged >75, three (0.8% of all AEs in this age group) and one (0.3%) SAEs had a possible and probable relation with the drug under study.
The figure shows the distribution of SAEs according to their relation with the drug under study.
Patients aged > 75 had more SAEs not related to safinamide (N=63, 17.0%) than patients aged ≤75 (N=83, 7.8%).
In paragraph 10.6 (see Table 39 of Final Statistical Report in Annex 1 - 6 Final Statistical Report) the complete distribution of serious adverse events in patients aged ≤75 and >75 associated with safinamide is shown.

Figure 10.5.1.3: 3 Serious adverse events: relation with safinamide (patients aged ≤75, >75 yrs)



Note. Percentages were computed out of the total number of AEs by patient age.

Considering the group of patients aged ≤75, for 92 SAEs (8.6%) no action was taken, while the drug was permanently interrupted for 20 (1.9%) SAEs and the drug was temporarily interrupted for four (0.4%) SAEs.
Considering the group of patients aged >75, for 64 SAEs (17.3%) no action was taken, while drug was permanently interrupted for seven (1.9%) SAEs, dosage was reduced for two (0.5%) SAEs and the drug was temporarily interrupted for one (0.3%) SAE.
The distribution of serious adverse events by action taken and age group is shown in Table 41 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report); in this table events are classified by SOC and PT.

10.5.1.4. Non-serious adverse events

During the study, 1241 non-serious adverse events occurred, 945 in patients aged ≤ 75 (88.7% of all AEs in this age group) and 296 (80.0%) in patients aged > 75.
The most frequently reported AEs were nervous system disorders (in older patients:N=102, 27.6% and in patients aged ≤ 75: N=349, 32.8%) and psychiatric disorders (in older patients: N=49, 13.2% and in patients aged ≤ 75: N=138, 13.0%).
In **Figure 10.5.1.4: 1** all non-serious AEs are described according to SOC in patients aged ≤ and >75. No relevant differences were observed in distribution between the two age groups.
The detailed distribution of all non-serious adverse events by SOC and PT in patients aged ≤75 and >75 is shown in Table 33 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).

10.5.1.5. Special Safety Situations

Out of the 1065 total adverse events during the study in patients aged ≤75, 14 (1.3%) were special safety situations in 10 patients. In six cases there was a suspected drug interaction, in four cases a lack of efficacy and in one case both suspected drug interaction and lack of efficacy; one episode of medication error for safinamide, one episode of occupational exposure to safinamide and one episode of off-label use of safinamide, occurred too.
In patients aged >75 years, no special situations occurred.
The listing of adverse events related to a special safety situation is shown in Table 43 of Final Statistical Report (see Annex 1 - 6 Final Statistical Report). The age of patients is stated in the listing and, as mentioned before, all events occurred in patients aged ≤75.

As declared by investigators, 80 (7.7%), 55 (5.5%) and 33 (3.3%) patients aged ≤75 had at least one special safety situation at 4-month, 8-month and 12-month follow-up, respectively. In older patients, the frequencies were 14 (4.1%), 13 (4.0%) and 9 (2.8%) at 4-month, 8-month and 12-month follow-up.
In **Table 10.5.1.5: 1** the detail of these special situations is shown.

Table 10.5.1.5: 1 Special safety situations during observation as declared by investigator (patients aged ≤75, >75)

	Total evaluable patients at 4-month		Total evaluable patients at 8-month		Total evaluable patients at 12-month	
	Pts aged ≤75 (N= 1033)	Pts aged >75 (N= 340)	Pts aged ≤75 (N= 1000)	Pts aged >75 yrs (N= 323)	Pts aged ≤75 (N= 1000)	Pts aged >75 (N= 326)
Patients with at least one special safety situation at follow-up	80 (7.7%)	14 (4.1%)	55 (5.5%)	13 (4.0%)	33 (3.3%)	9 (2.8%)
Overdose	1 (1.3%)	1 (7.1%)	0 (0.0%)	0 (0.0%)	1 (3.0%)	0 (0.0%)
Misuse	1 (1.3%)	2 (14.3%)	0 (0.0%)	1 (7.7%)	0 (0.0%)	0 (0.0%)
Lack of efficacy	30 (37.5%)	5 (35.7%)	14 (25.5%)	5 (38.5%)	9 (27.3%)	4 (44.4%)
Suspected drug interaction with safinamide	5 (6.3%)	1 (7.1%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	1 (11.1%)
Episode of off-label use of safinamide	50 (62.5%)	7 (50.0%)	42 (76.4%)	8 (61.5%)	23 (69.7%)	4 (44.4%)
Episode of medication error of safinamide	1 (1.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Note. Percentages of patients with at least one special safety situation at follow-up are computed out of the total number of of patients evaluable for FAS and 4-, 8- or 12-month follow up by patient age.
Note. Percentages of special safety situatiotions are computed out of the total number of patients evaluable for FAS and 4-, 8- or 12-month follow-up with at least one special safety situation by patient age. The same patient could have more than one special safety situation.

10.5.2 Patients with relevant comorbidities

10.5.1.1. Safinamide treatment patterns

The Safinamide initial daily dose was one 50-mg tablet in 1041 (94.4%) patients with relevant comorbidities and 411 (90.3%) patients without comorbidities.

The 100-mg daily dose (either as one tablet or two tablets) was administered as starting dose to 60 patients (5.4%) with relevant comorbidities and to 36 patients (7.9%) without relevant comorbidities.

In patients with relevant comorbidities, one patient (0.1%) received 1/2 50-mg tablet (i.e. 25 mg daily dose) and another (0.1%) received 1/4 50-mg tablet (i.e. 12.5 mg daily dose). In patients without relevant comorbidities, six (1.3%) patients were administered 1/2 50-mg tablet (i.e. 25 mg daily dose), one (0.2%) 1/2 100-mg tablet (i.e. 50 mg daily dose) and one (0.2%) 1/4 50-mg tablet (i.e. 12.5 mg daily dose).

Dose change was observed for 652 patients (59.1%) with relevant comorbidities and for 256 (56.3%) patients without relevant comorbidities.

Safinamide temporary discontinuation was observed for 46 (4.2%) and 22 (4.8%) patients with or without relevant comorbidities, respectively.
During the study, 237 (21.5%) and 99 (21.8%) evaluable patients with or without relevant comorbidities respectively, permanently discontinued safinamide. Main reasons for discontinuation in patients with relevant comorbidities were: adverse reaction (N=116, 48.9%), patient choice (N=57, 24.1%), disease progression (N=16, 6.8%) and other reasons (N=48, 20.3%). In patients without relevant comorbidities, main reasons for discontinuation were: adverse reaction (N=45, 45.5%), patient choice (N=24, 24.2%), disease progression (N=4, 4.0%) and other reasons (N=26, 26.3%).

10.5.1.2. Adverse events

As shown in **Table 10.5.2.1:1**, during the observation period 542 (49.1%) patients with relevant comorbidities had at least one AE (total number of AEs: 1151) and 315 patients (28.6%) had at least one ADR (total number of ADRs: 517); 122 (11.1%) patients had at least one SAE and 28 patients (2.5%) at least one SADR.
The total number of SAEs and SADRs in this subpopulation were 169 and 40, respectively.
It is worth noting that the proportion of patients with AEs and SAEs is lower in patients without relevant comorbidities (N=172, 37.8% and N=21, 4.6%, respectively) than in patients with relevant comorbidities.

Table 10.5.2.1:1 Adverse events and adverse reactions during observation period by relevant comorbidities:

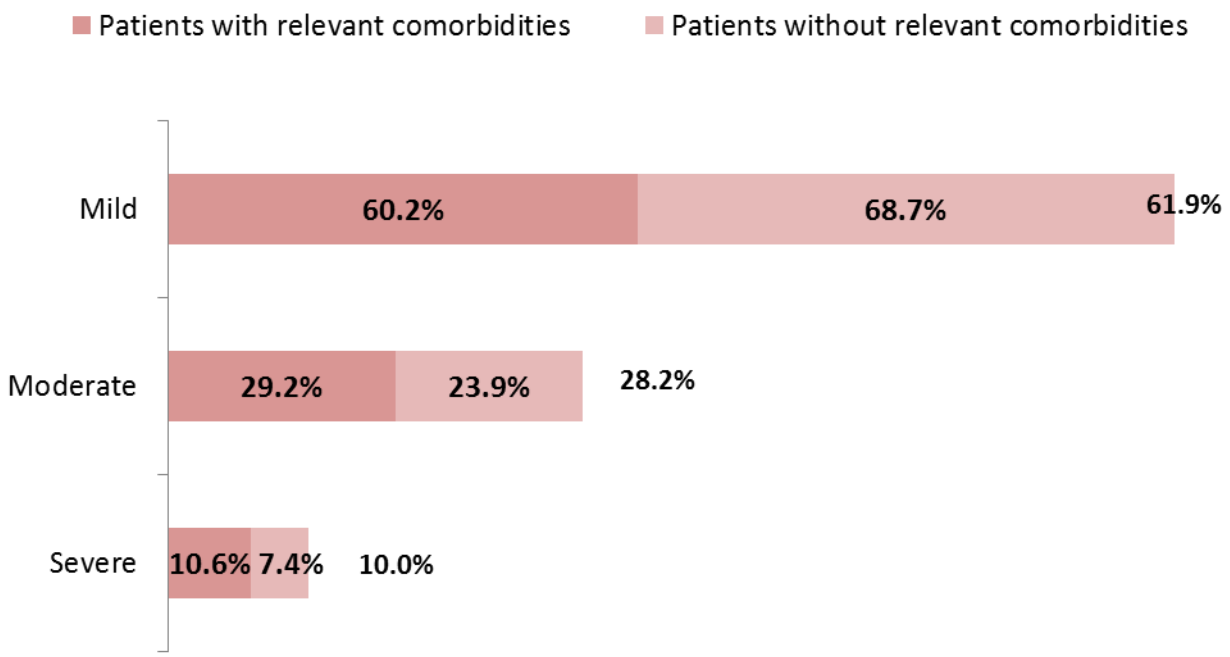
	Patients with relevant comotbidities (N=1103)	**Patients without relevant comorbidities (N=455)**	**Total number of patients evaluable for the FAS (N=1558)**
Patients with at least one AE (N, %)	542 (49.1%)	172 (37.8%)	714 (45.8%)
Patients with at least one SAE (N, %)	122 (11.1%)	21 (4.6%)	143 (9.2%)
Patients with at least one ADR (N, %)	315 (28.6%)	117 (25.7%)	432 (27.7%)
Patients with at least one SADR (N, %)	28 (2.5%)	8 (1.8%)	36 (2.3%)
Total number of AEs (N)	1151	284	1435

	Patients with relevant comotbidities (N=1103)	Patients without relevant comorbidities (N=455)	Total number of patients evaluable for the FAS (N=1558)
Total number of SAEs (N)	169	25	194
Total number of ADRs (N)	517	168	685
Total number of SADRs (N)	40	8	48

Note. Percentages are computed out of the total number of patients by age group.
AE: Adverse Event. ADR: Adverse Drug Reaction. SADR: Serious Adverse Drug Reaction. SAE: Serious Adverse Event.

As regards severity, **Figure 10.5.2.1: 2**, in patients with relevant comorbidities the frequency of severe events (N=122, 10.6%) is higher than in patients without relevant comorbidities (N=21, 7.4%).
The detailed distribution of adverse events severity by SOC and PT in patients with and without comorbidities is shown in Table 35B of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).

Figure 10.5.2.1: 2 Severity of AEs between patients with or without relevant comorbidities

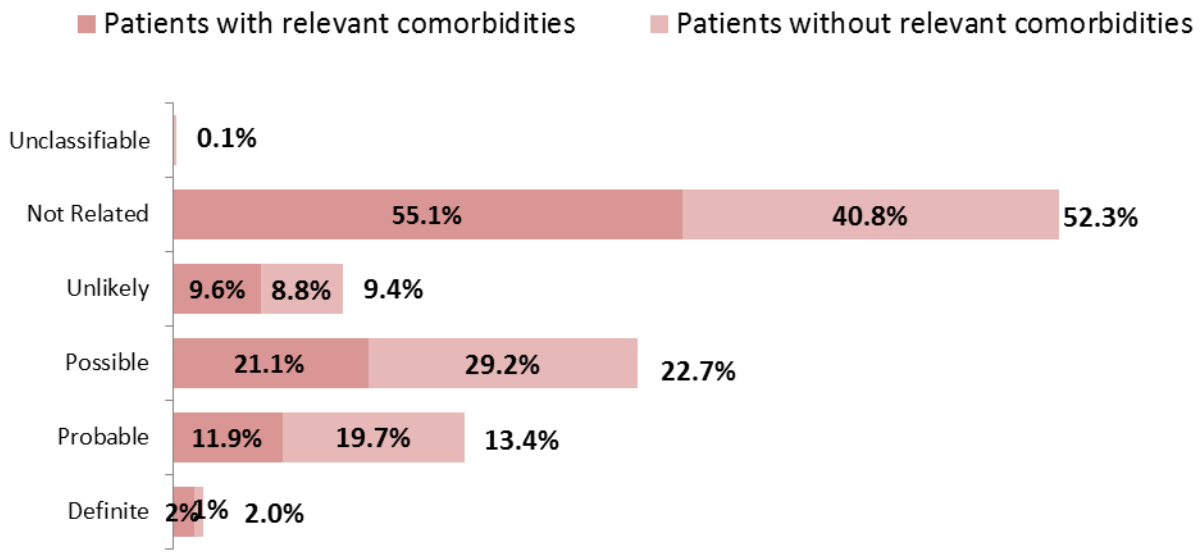


Note. Percentages were computed out of the total number of AEs by patient group

As shown in **Figure 10.5.2.1: 3** the proportion of events not related with safinamide was higher in patients with relevant comorbidities (N=634, 55.1% of total number of occurred events in this sub group) than in patients without relevant comorbidities (N=116, 40.8%). In those with

relevant comorbidities 26 (2.3%), 137 (11.9%) and 243 (21.1%) events had a definite, probable and possible relation with the drug under study, respectively. Specifically, seven (0.6%) dyskinesias, two (0.2%) agitation and two (0.2%) hallucination events were observed in patients with relevant comorbidities which had definite relation with safinamide. In patients without relevant comorbidities, three (1.1%) events were considered to have a definite relation with safinamide, 56 (19.7%) a probable relation and 83 (29.2%) a possible relation.
The distribution of adverse events by causal relationship with safinamide is shown in patients aged with and without comorbidities in Table 38B of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report); in the table events are classified by SOC and PT.

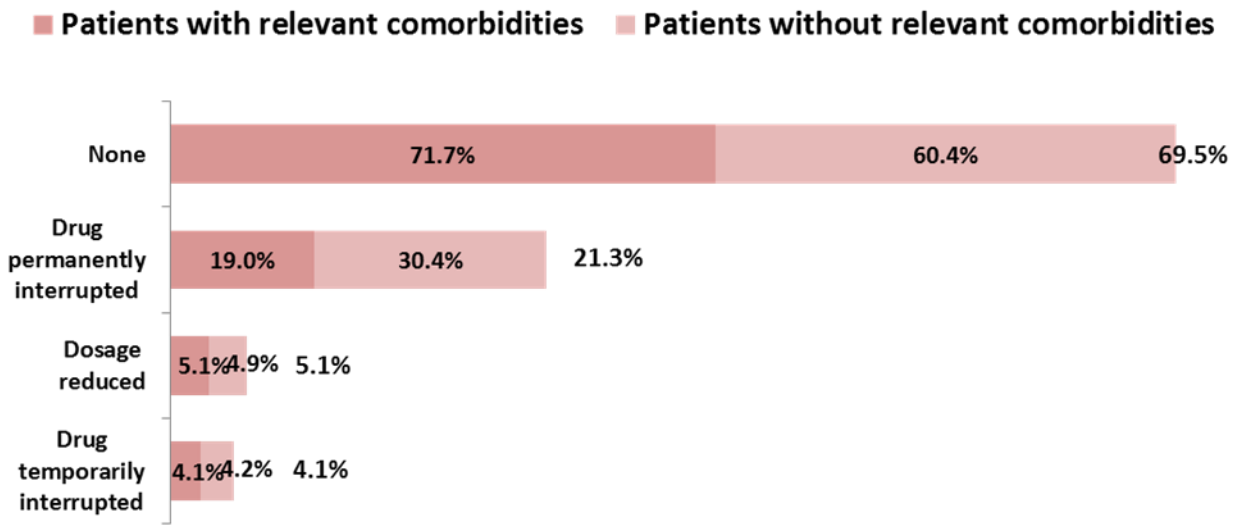
Figure 10.5.2.1:3 Adverse events in relation to safinamide (by relevant comorbidities):



Note. Percentages were computed out of the total number of AEs by patient group

Considering the 1151 adverse events in patients with relevant comorbidities (as shown in **Figure 10.5.2.1: 4**) for 822 AEs (71.4%) no action was takenwhile, drug was permanently interrupted for 218 (18.9%) adverse events; the dosage was reduced for 59 (5.1%) events and the drug was temporarily interrupted for 47 (4.1%) events. This distribution was slightly different in patients without comorbidities, with 171 (60.2%) events with no action taken and 86 (30.3%) events that led to safinamide permanent discontinuation.

Figure 10.5.2.1: 4 Action taken with safinamide in response to an adverse event (by relevant comorbidities)



Note. Percentages were computed out of the total number of AEs by patient group

AEs causing safinamide permanent interruption in the Nervous system disorders SOC were 78 (6.8%) in patients with relevant comorbidities, and 28 (9.9%) in patients without relevant comorbidities; 47 (4.1%) and 17 (6.0%) in the Psychiatric disorders SOC in patients with and without relevant comorbidities, respectively. Moreover, 23 (2.0%) events in the Gastrointestinal disorders SOC led to permanent discontinuation in patients with relevant comorbidities, versus 4 (1.4%) in patients without relevant comorbidities. Finally, patients without relevant comorbidities experienced 10 (3.5%) AEs in the General disorders SOC that led to permanent discontinuation vs 23 (2.0%) patients with relevant comorbidities (mostly gait disturbance and ineffective drug).

The distribution of occurred adverse events by action taken in patients with or without relevant comorbidities is shown in Table 40B of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report); in the table events are classified by SOC and PT.

The outcome of the 1151 adverse events in patients with relevant comorbidities was as follows: recovered/resolved in 656 (57.0%) events, not recovered/not resolved in 276 (24.0%) events, recovering/resolving in 106 (9.2%) events, fatal in 23 (2.0%) cases and recovered/resolved with sequelae in nine (0.8%) cases.
Similar proportions were observed in the group of patients without relevant comorbidities for the number of events recovered/resolved and recovering/resolving (N=168, 59.2% and N=26, 9.2%, respectively). Higher proportion of recovered/resolved with sequelae events (N=8, 2.8%) was observed in this group respect to patients with relevant comorbidities. Lower proportion of not recovered/not resolved events (N=54, 19%) was observed in patients without respect to with relevant comorbidities. Lastly, one patient (0.4%) had a fatal outcome in the group of patients without relevant comorbidities.
As for dyskinesia, 127 (11.5%) and 56 (12.3%) patients with or without relevant comorbidities respectively, had at least one adverse event of dyskinesia (total number of AEs related to

dyskinesia N=141, and 56 in patients with or without relevant comorbidities respectively).

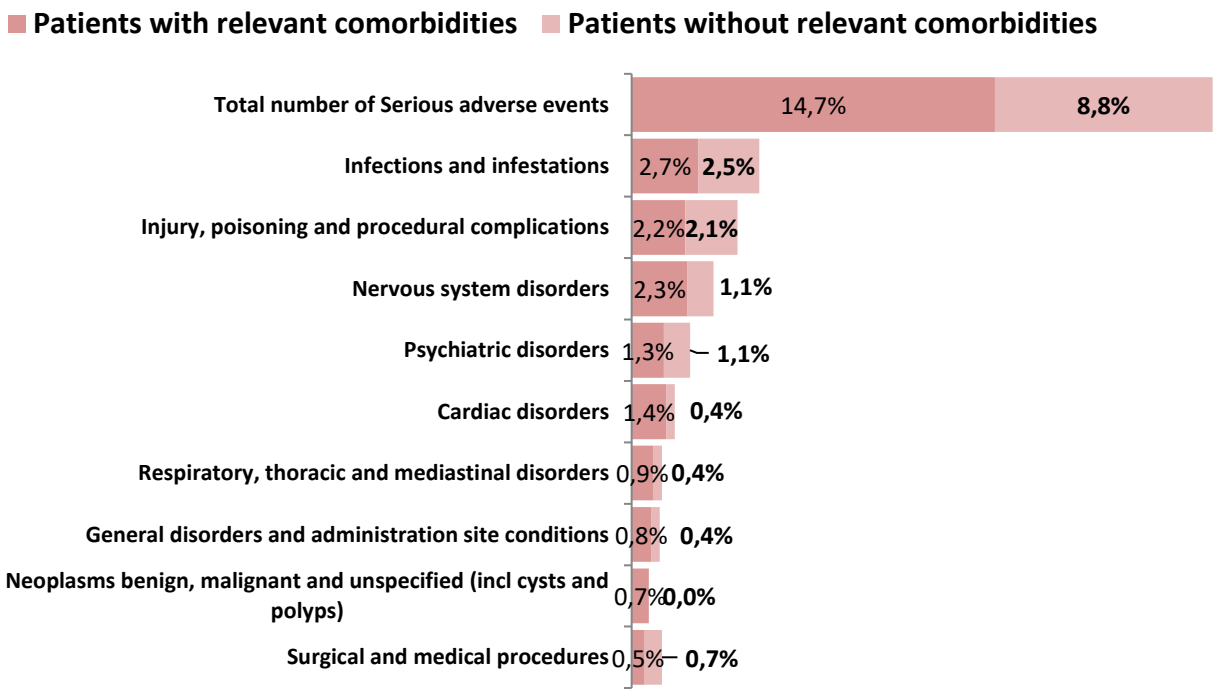
10.5.2.2 Serious adverse events

Among patients with relevant comorbidities, 169 (14.7%) serious adverse events were reported, while there were 25 (8.8%) in patients without relevant comorbidities.

Seriousness criteria for SAEs in patients with relevant comorbidities were new/prolonged hospitalization(s) (N=129, 11.2%), fatal (N=23, 2.0%), other important medical event(s) (N=11, 1.0%), resulted in persistent/significant disability/incapacity (N=3, 0.3%) and life-threatening (N=3, 0.3%).
Seriousness criteria for SAEs in patients without relevant comorbidities were: new/prolonged hospitalization(s) (N=19, 6.7%), other important medical event(s) (N=3, 1.1%), resulted in persistent/significant disability/incapacity (N=2, 0.7%) and fatal (N=1, 0.4%).

The most frequently reported (frequency ≥1%) SAEs in patients with relevant comorbidities were in the Infections and infestations SOC (N=31, 2.7%), Nervous system disorders (N=26, 2.3%), Injury, poisoning and procedural complications (N=25, 2.2%) and Psychiatric disorders (N=15, 1.3%), while the most frequently reported ones in patients without relevant comorbidities were in the Infections and infestations (N=7, 2.5%), Injury, poisoning and procedural complications (N=6, 2.1%), and Nervous system disorders (N=3, 1.1%) SOCs.

Figure 10.5.2.2: 1 Serious adverse events: System Organ Class (patients with/without relevant comorbidities)



Note. Percentages were computed out of the total number of AEs by patient age

Considering patients with relevant comorbidities, the 31 SAEs in the Infections and Infestations SOC included: Pneumonia (N=9), urinary tract infection (N=5), lung infection (N=3), respiratory tract infection (N=3), Escherichia sepsis (N=2), cellulitis (N=1), diarrhea infectious (N=1), infection (N=1), influenza (N=1), lower respiratory tract infection (N=1), pneumonia bacterial (N=1), retroperitoneal abscess (N=1), sepsis (N=1), varicella zoster virus infection (N=1).

The detailed distribution of all serious adverse events (by SOC and PT) in patients with and without comorbidities is shown in Table 33B of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).
.

In the group of patients with relevant comorbidities, six (0.5%) and one (0.1%) SAE had a possible and probable relation with safinamide respectively. In the group of patients without relevant comorbidities, two (0.7%) and three (1.1%) SAEs had a possible and probable relation with the drug under study, respectively. SAEs with unlikely relation were 35, three of which in patients without relevant comorbidities and the remaining in patients with relevant comorbidities.
Patients with relevant comorbidities had more SAEs not related to safinamide (N=129, 11.2%) than patients without relevant comorbidities (N=17, 6.0%).

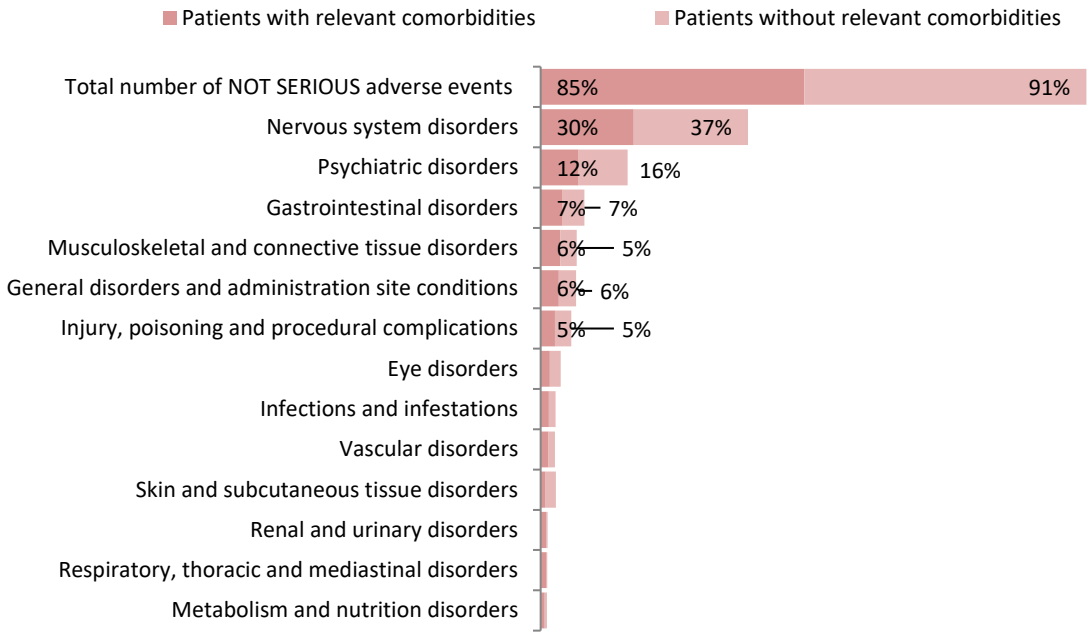
10.5.2.3 Non-serious adverse events

During the study, 982 (85.3%) non-serious adverse events were reported in patients with relevant comorbidities and 259 (91.2%) in patients without relevant comorbidities.

The most frequent non-serious adverse events were in the Nervous system disorders SOC (N=346, 30.1%, in patients with relevant comorbidities; N=105, 37.0%, in patients without relevant comorbidities) and Psychiatric disorders SOC (N=142, 12.3%, in patients with relevant comorbidities; N=45, 15.8%, in patients without relevant comorbidities).

Figure 10.5.2.3:1 summarizes all non serious AEs in patients with or without relevant comorbidities arranged by SOC. No relevant differences were observed in distribution between the two age groups.

Figure 10.5.2.3: 1 Non-serious adverse events: System Organ Class (patients with/without relevant comorbidities)



Note: Percentages were computed out of the total number of occurred non serious adverse events by patient relevant comorbidities. Only >=5% frequencies are shown

The detailed distribution of all non-serious adverse events by SOC and PT in patients with or without relevant comorbidities is shown in Table 33B of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).

10.5.2.4 Special Safety Situations

Out of 1151 total adverse events during the study in patients with relevant comorbidities, 12 (1.0%) were special safety situations, two of which were serious adverse events, namely one parkinsonism due to medication error and one urinary retention due to suspected drug interaction with safinamide.
In the sample of patients without relevant comorbidities, two special safety situations were recorded, one of which involved serious dyskinesia due to an off-label use of safinamide.

10.5.3 Patients with psychiatric conditions

10.5.3.1 Safinamide treatment patterns

No relevant differences emerged in the safinamide initial daily dose by patients with or without psychiatric conditions; at the start of treatment, the majority of patients (N=616, 93.2% in patients with psychiatric conditions and N=836, 93.2% in patients without psychiatric conditions) were administered a daily dose of one tablet (50 mg).

One 100-mg tablet was administered as starting dose to 41 patients (6.2%) with psychiatric conditions and to 53 patients (5.9%) without psychiatric conditions. Moreover, two (0.2%) patients without psychiatric conditions received two tablets (100 mg) as starting daily dose.

In the group of patients with psychiatric conditions, three (0.5%) and one (0.2%) patients were administered ½ 50-mg tablet (i.e. 25 mg daily dose) and ¼ tablet (i.e. 12.5 mg daily dose), respectively. In patients without psychiatric conditions, four (0.4%), one (0.1%) and one (0.1%) patients were administered with ½ tablet (i.e. 25 mg daily dose), ¼ tablet (i.e. 12.5 mg daily dose), and ½ tablet (i.e. 50 mg daily dose) respectively.

During the study, 164 (24.8%) and 172 (19.2%) evaluable patients with or without psychiatric conditions respectively, permanently discontinued safinamide. The main reasons for discontinuation in patients with psychiatric conditions were: adverse reaction (N=82, 50%), patient choice (N=39, 23.8%), disease progression (N=13, 7.9%) and other reasons (N=30, 18.3%). In patients without psychiatric conditions, main reasons for discontinuation were: adverse reaction (N=79, 45.9%), patient choice (N=42, 24.4%), disease progression (N=7, 4.1%) and other reasons (N=44, 25.6%).

10.5.3.2 Adverse events

As reported in **Table 10.5.3.2:1**, during observation, 316 (47.8%) patients with psychiatric conditions had at least one AE (total number of AEs: 653) and 205 patients (31.0%) had at least one ADR (total number of ADRs: 352); 68 (10.3%) patients had at least one SAE and 23 patients (3.5%) at least one SADR.
The total number of SAEs and SADRs in this subpopulation were 100 and 31, respectively.
The proportion of patients with ≥1 ADRs in patients without psychiatric conditions is 25.3% (N=227) amounting to a total of 333 ADRs.

Table 10.5.3.2: 1 Adverse events and adverse reactions during the observation period by psychiatric conditions:

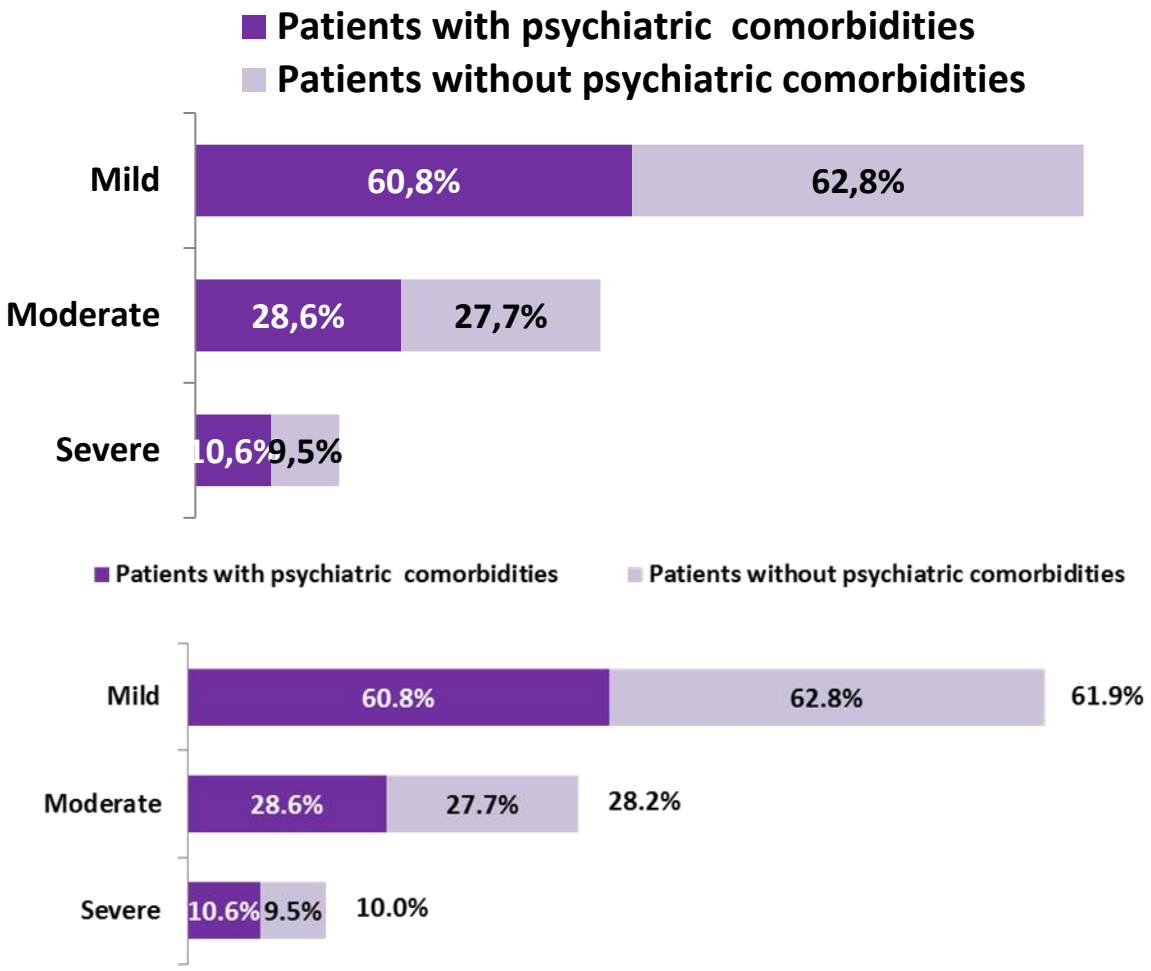
	Patients with psychiatric conditions (N=661)	Patients without psychiatric conditions (N=897)	Total number of patients evaluable for the FAS (N=1558)
Patients with at least one AE (N, %)	316 (47.8%)	398 (44.4%)	714 (45.8%)
Patients with at least one SAE (N, %)	68 (10.3%)	75 (8.4%)	143 (9.2%)
Patients with at least one ADR (N, %)	205 (31.0%)	227 (25.3%)	432 (27.7%)
Patients with at least one SADR (N, %)	23 (3.5%)	13 (1.4%)	36 (2.3%)
Total number of AEs (N)	653	782	1435

	Patients with psychiatric conditions (N=661)	Patients without psychiatric conditions (N=897)	Total number of patients evaluable for the FAS (N=1558)
Total number of SAEs (N)	100	94	194
Total number of ADRs (N)	352	333	685
Total number of SADRs (N)	31	17	48

Note. Percentages are computed out of the total number of patients by age group.
AE: Adverse Event. ADR: Adverse Drug Reaction. SADR: Serious Adverse Drug Reaction. SAE: Serious Adverse Event.

As for severity, as depicted in **Figure 10.5.3.2:2**, in patients with psychiatric conditions the frequency of severe events (N=69, 10.6%) was similar to the one observed in patients without psychiatric conditions (N=74, 9.5%).

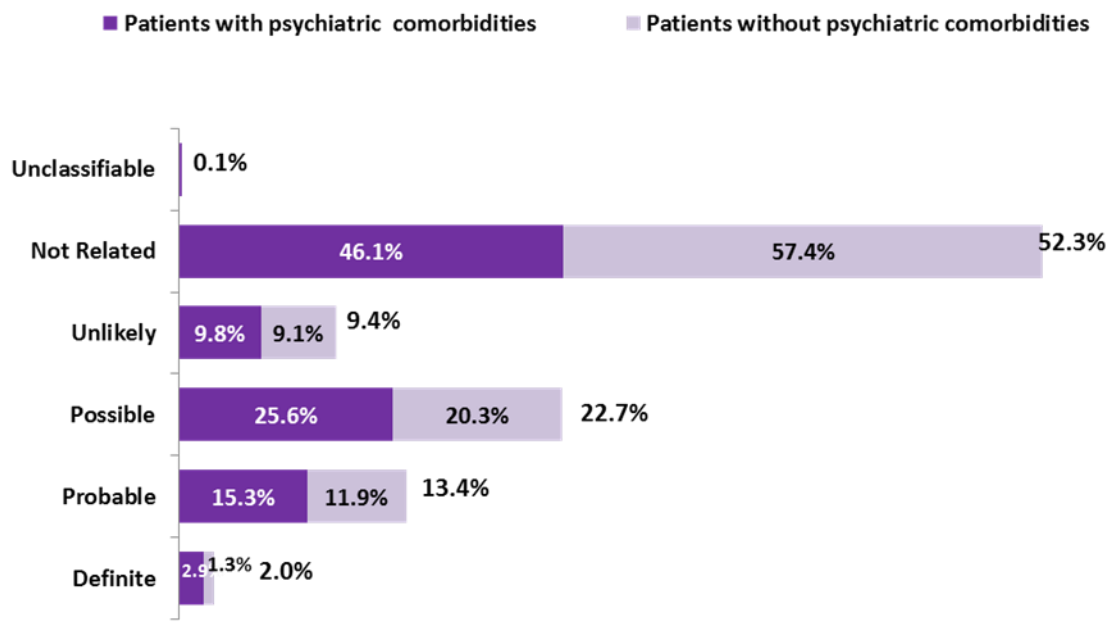
Figure 10.5.3.2:2 Severity of AEs between patients with or without psychiatric conditions



Considering the total number of events in patients with psychiatric conditions (N=653) and patients without psychiatric conditions (N=782), as shown in **Figure 10.5.3.2:3**, the proportion

of events not related with safinamide was lower in patients with psychiatric conditions (N=301, 46.1% of total number of occurred events in this sub group) than in patients without psychiatric conditions (N=449, 57.4%). In patients with psychiatric conditions 19 (2.9%), 100 (15.3%) and 167 (25.6%) events had a definite, probable and possible relation with the drug under study respectively.

Figure 10.5.3.2:3 Adverse events relation with safinamide (by psychiatric conditions):

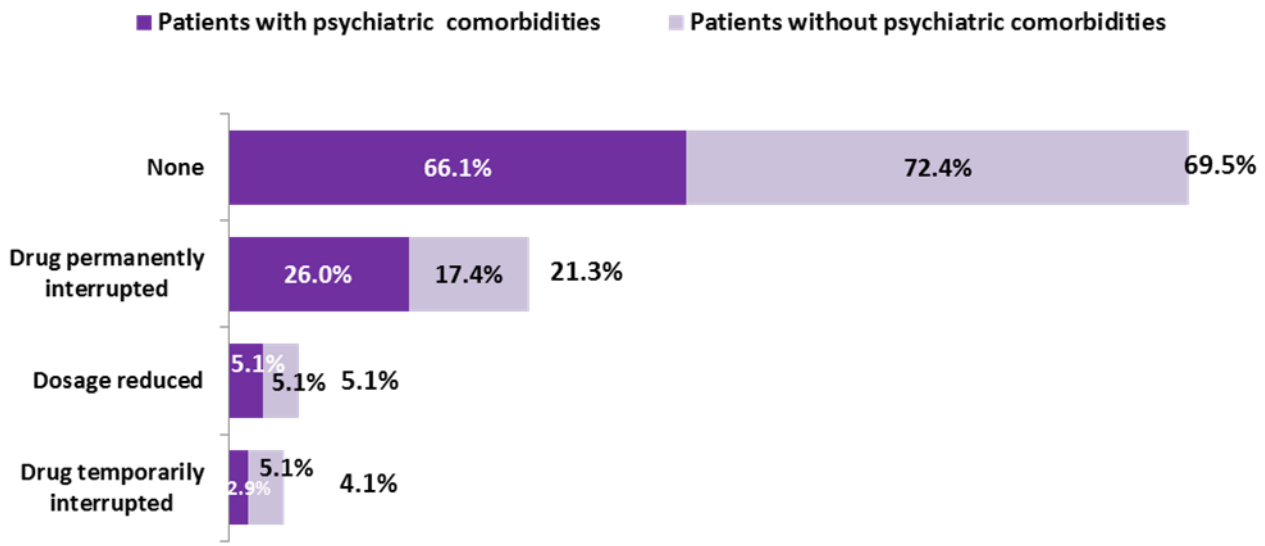


Note. Percentages were computed out of the total number of AEs by patient group

In patients with psychiatric conditions, for 430 AEs (65.8%) no action was taken; instead, drug was permanently interrupted for 169 (25.9%) adverse events; the dosage was reduced for 33 (5.1%) events and the drug was temporarily interrupted for 19 (2.9%) events.

Figure 10.5.3.2:4 shows the action taken with safinamide in response to adverse events by psychiatric conditions.

Figure 10.5.3.2:4 Action Taken to adverse events (by psychiatric conditions)



Note. Percentages were computed out of the total number of AEs by patient group

The distribution of adverse events by action taken in patients with or without psychiatric conditions is shown in Table 40C of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report); in the table events are classified by SOC and PT.

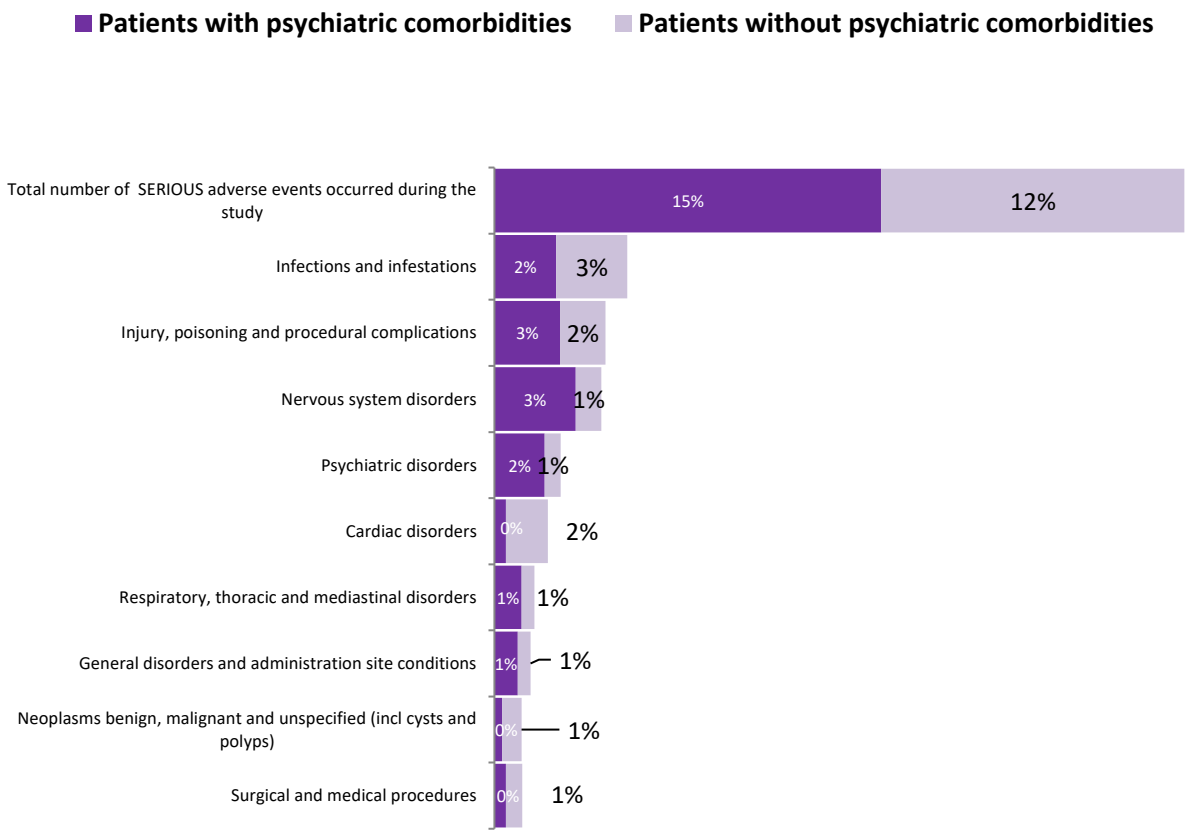
The outcome of the 653 adverse events in patients with psychiatric conditions was as follows: recovered/resolved for 400 (61.3%) events, not recovered/not resolved for 143 (21.9%) events, recovering/resolving for 47 (7.2%) events, fatal for nine (1.4%) events and recovered/resolved with sequelae for seven (1.1%) events.
The outcome of the 782 occurred adverse events in patients without psychiatric conditions was recovered/resolved for 424 (54.2%) events, not recovered/not resolved for 187 (23.9%) events, recovering/resolving for 85 (10.9%) events, fatal for 15 (1.9%) events and recovered/resolved with sequelae for 10 (1.3%) events.

10.5.3.3 Serious adverse events

Among patients with psychiatric conditions 100 (15.3%) serious adverse events occurred in 68 (10.3%) patients, while in patients without psychiatric conditions There were 94 (12.0%) SAEs experienced by 75 (8.4%) patients.

The most frequently reported (frequency ≥1%) SAEs in patients with psychiatric conditions were in the Injury, poisoning and procedural complications (N=17, 2.6%), Infections and infestations (N=16, 2.5%), Nervous system disorders (N=21, 3.2%) and Psychiatric disorders (N=13, 2.0%) SOCs, while the most frequently reported SAEs in patients without psychiatric conditions were in the Infections and infestations (N=22, 2.8%), Injury, poisoning and procedural complications (N=14, 1.8%), and Nervous system disorders (N=8, 1.0%) SOCs.

Figure 10.5.3.3: 1 Serious adverse events: System Organ Class (patients with/without psychiatric conditions)



Note. Percentages were computed out of the total number of AE by patient age

Considering patients with psychiatric conditions, the 17 events in the SOC Injury, poisoning and procedural complications, included the following: hip fracture (N=3), femur fracture (N=3), fall (N=2), humerus fracture (N=1), upper limb fracture (N=1), brain contusion (N=1), pelvic fracture (N=1), skin injury (N=1), femoral neck fracture (N=1), fibula fracture (N=1), anaemia postoperative (N=1), toxicity to various agents (N=1).

The 16 events in the SOC Infections and Infestations, included the following: Pneumonia (N=3), lung infection (N=3), urinary tract infection (N=2), respiratory tract infection (N=2), intervertebral discitis (N=1), staphylococcal bacteraemia (N=1), staphylococcal meningitis (N=1), staphylococcal infection (N=1), pneumonia bacterial (N=1), infection (N=1).

Fatal outcome was observed for 9 SAEs (1.4%) in patients with psychiatric conditions and 15 SAE (1.9%) in patients without psychiatric conditions.

In the group of patients with psychiatric conditions 6 SAEs (0.9%) and 4 (0.6%) SAEs had a possible and probable relation with safinamide, respectively; moreover 20 SAEs were unlikely related and one was unclassifiable. In the group of patients without psychiatric conditions two and 15 SAEs (0.3%) had a possible and unlikely relation with the drug under study, respectively. Patients with psychiatric conditions had 69 (10.6%) SAEs not related to safinamide, in patients without psychiatric conditions SAEs not related to safinamide were 77 (9.8%).

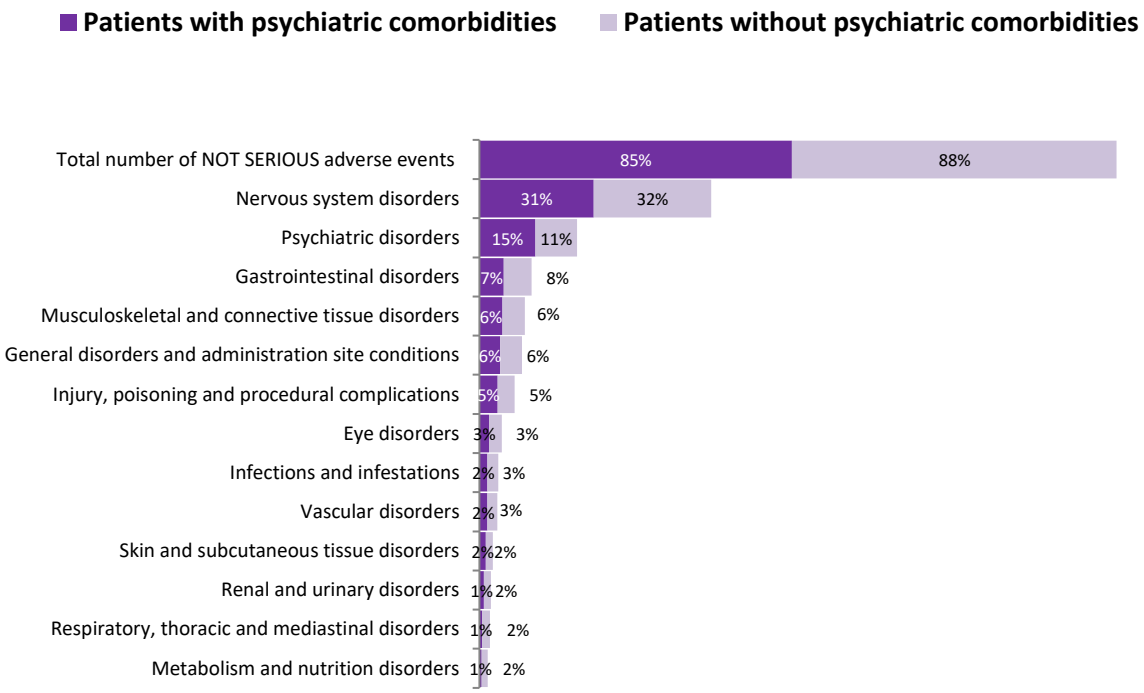
10.5.3.4 Non serious adverse events

Patients with psychiatric conditions experienced 553 (84.7%) non serious adverse events, while patients without psychiatric conditions experienced 688 (88.0%) non-serious adverse events.

The most frequent AEs were in the Nervous system disorders (in patients with psychiatric conditions: N=202, 30.9% and in patients without psychiatric conditions: N=249, 31.8%) and Psychiatric disorders (in patients with psychiatric conditions :N=99, 15.2% and in patients without psychiatric conditions: N=88, 11.3%) SOCs.

In **Figure 10.5.3.4: 1** all non-serious AEs are described according to SOC in patients with or without psychiatric conditions. No relevant differences were observed in distribution between the two subgroups.

Figure 10.5.3.4: 1 Non-serious adverse events: System Organ Class (patients with/without psychiatric conditions)



Note. Percentages were computed out of the total number of non-serious adverse events by patient relevant comorbidities.

The detailed distribution of all non-serious adverse events by SOC and PT in patients with or without relevant comorbidities is shown in Table 33C of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).

10.5.3.5 Special Safety Situations

Out of the 653 total adverse events during the study in patients with psychiatric conditions, 10 (1.5%) were special safety situations. In five cases there was a suspected drug interaction; in two cases a lack of efficacy and in another both suspected drug interaction and lack of efficacy; one episode of medication error of safinamide, and one episode of off-label use of safinamide occurred, too.

On the other hand, in people without psychiatric conditions, four (0.5%) events were special safety situations. In two cases, there was a lack of efficacy; in one case there was a suspected drug interaction, and there was one episode of occupational exposure to safinamide.

The listing of adverse events related to a special safety situation is in Table 43 of the Final Statistical Report (see Annex 1 - 6 Final Statistical Report).

10.5.4 Sensitivity analysis

Patients with a partially retrospective observation period (having started treatment with safinamide before study inclusion) were 779 (50% of evaluable patients). The proportion of patients experiencing any adverse event among patients who started safinamide before or after study inclusion was provided as sensitivity analysis.

As shown in **Table 10.5.4:1**, during observation, 348 (44.7%) patients under partially retrospective observation experienced 703 AEs and 190 (24.4%) patients had 314 ADRs. Seventy-five (9.6%) patients had at least one SAE during observation and 20 patients (2.6%) at least one SADR. The total number of SAEs and SADRs in this subpopulation were 104 and 30respectively. Out of 779 patients under prospective observation, 47% (N=366) experienced in total 732 AEs and 242 (31.1%) patients experienced in total 371 ADR; 68 (8.7%) had 90 SAEs during observation and 16 patients (2.1%) had 18 SADRs.

Table 10.5.4: 1 Adverse events and adverse reactions during the observation period by patient status (partially retrospective vs prospective):

	Partially Retrospective Patients (N= 779)	**Prospective Patients (N= 779)**
Patients with at least one adverse event (AE) (N, %)	348 (44.7%)	366 (47.0%)
Patients with at least one Serious adverse event (SAE) (N, %)	75 (9.6%)	68 (8.7%)
Patients with at least one Adverse Drug Reaction (ADR) (N, %)	190 (24.4%)	242 (31.1%)
Patients with at least one serious adverse drug reaction (SADR) (N, %)	20 (2.6%)	16 (2.1%)
Total number of Adverse Events (N)	703	732
Total number of Serious Adverse Events (N)	104	90
Total number of Adverse Drug Reactions (N)	314	371
Total number of Serious Adverse Drug Reaction (N)	30	18

Note. Percentages are computed out of the total number of patients evaluable at enrollment by status (partially retrospective and prospective status)

10.6. Adverse events/adverse reactions

As reported in chapter 10.4, during observation, 714 (45.8%) patients experienced in total 1435 AEs and 432 (27.7%) patients experienced in total 685 ADRs; 134 patients (9.2%) experienced 194 SAEs and 36 patients (2.3%) experienced 48 SADRs.

The following tables (see Final Statistical Report, Annex 1 - *6 Final Statistical Report*) were produced, each one exploring different features of the adverse events (seriousness, severity, outcome, etc..).
Adverse events in each table were classified in System Organ Class and Preferred term.

AEs: severity

- Table 35. Description of adverse events during observation by severity (AE-based analysis) by patient age
- Table 35B. Description of adverse events during observation by severity (AE-based analysis) by relevant comorbidities
- Table 35C. Description of adverse events during observation by severity (AE-based analysis) by psychiatric conditions

AEs: outcome

- Table 36. Description of adverse events during observation by outcome (AE-based analysis) by patient age
- Table 36B. Description of adverse events during observation by outcome (AE-based analysis) by relevant comorbidities
- Table 36C. Description of adverse events during observation by outcome (AE-based analysis) by psychiatric conditions

AEs: action taken with safinamide

- Table 40. Action taken with safinamide in response to the event during observation(AE-based analysis) by patient age
- Table 40B. Action taken with safinamide in response to the event during observation(AE-based analysis) by relevant comorbidities
- Table 40C. Action taken with safinamide in response to the event during observation(AE-based analysis) by psychiatric conditions

AEs: causal relationship with safinamide

- Table 38. Description of adverse events during observation by causal relationship with safinamide (AE-based analysis) by patient age
- Table 38B. Description of adverse events during observation by causal relationship with safinamide (AE-based analysis) by relevant comorbidities
- Table 38C. Description of adverse events during observation by causal relationship with safinamide (AE-based analysis) by psychiatric conditions

AEs: seriousness

- Table 33. Description of adverse events during observation by seriousness (AE-based analysis) by patient age
- Table 33B. Description of adverse events during observation by seriousness (AE-based

analysis) by relevant comorbidities
- Table 33C. Description of adverse events during observation by seriousness (AE-based analysis) by psychiatric condition
- Table 34. Description of serious adverse events during observation by seriousness classification criteria (AE-based analysis) by patient age
- Table 34B. Description of serious adverse events during observation by seriousness classification criteria (AE-based analysis) by relevant comorbidities
- Table 34C. Description of serious adverse events during observation by seriousness classification criteria (AE-based analysis) by psychiatric conditions

SAEs: outcome
- Table 37. Description of serious adverse events during observation by outcome (AE-based analysis) by patient age
- Table 37B. Description of serious adverse events during observation by outcome (AE-based analysis) by relevant comorbidities
- Table 37C. Description of serious adverse events during observation by outcome (AE-based analysis) by psychiatric conditions

SAEs: causal relationship with safinamide
- Table 39. Description of serious adverse events during observation by causal relationship with safinamide(AE-based analysis) by patient age
- Table 39B. Description of serious adverse events during observation by causal relationship with safinamide(AE-based analysis) by relevant comorbidities
- Table 39C. Description of serious adverse events during observation by causal relationship with safinamide(AE-based analysis) by psychiatric condition

Special situations
- Table 43. Listing of adverse events related to a special safety situation
- Table 45. Listing of serious adverse events related to a special safety situation

A detailed listing (see Table A3 – Annex 2.1) of SAEs was produced. It summarized the following information: patient age and gender, presence of relevant comorbidities (yes/no), presence of psychiatric conditions (yes/no), start date of safinamide, end date of safinamide/ ongoing at the end of observation (and in case of discontinuation, the corresponding reason), dose at start of safinamide, description of serious adverse events (SOC and PT), SAE start date, SAE date of resolution/ongoing at the end of observation, severity, criteria for seriousness, outcome, causal relationship with safinamide, action taken.

Among SAE, 24 were fatal, six unlikely to be related and the remaining not related. For 13 such events no action was taken, whereas for 11 safinamide was permanently interrupted. These fatal events were namely: eight infections (among which three pneumonia and two lung infections), five cardiac events, two cerebrovascular disorders, two gastrointestinal disorders, two suicides (one completed, one attempt), two respiratory disorders, one dehydration, one drowning, one death for unknown reason.

11. Discussion

In total, 1610 patients have been enrolled in the SYNAPSES study, and 1558 (96.8%) were evaluable for the analysis, with more than 80% followed up prospectively for one year.

The sample was composed by the following sub-groups which were of specific interest for the study: 25% patients older-than-75-years, 71% patients with relevant comorbidities and 42% with psychiatric conditions.

Mean (SD) age at enrollment was 68.4 (9.7) years. Patients without relevant comorbidities were five years younger than those with comorbidities (64.6 (10.7) vs 70 (8.7) years), while no difference was observed between patients with vs without psychiatric conditions (68.3 (9.4) vs 68.5 (9.9) years). Overall, 37.1% (N=516) of patients had H&Y stage > 2, while in the subpopulations the proportions were 56.0% (patients with age > 75 years), 40.2% (patients with relevant comorbidities) and 46.2% (patients with psychiatric conditions). Lower H&Y stages were observed for younger patients (vs older ones), for patients without (vs patients with) relevant comorbidities and for patients without (vs patients with) psychiatric conditions.
Older patients showed a higher frequency of tremor, postural instability and cognitive symptoms than younger patients. No relevant differences for fluctuations were observed according to age. This reflects what is clinically expected in PD patients according to age.
Patients with comorbidities had similarities to elderly patients: they showed higher disease severity and tremor. Postural instability and non-motor symptoms were more frequent in patients with relevant comorbidities than in those without.
Patients with psychiatric conditions had higher disease severity, higher frequency of postural instability and higher frequency of non-motor symptoms than patients without psychiatric conditions.

11.1. Key results

Safinamide was administered at an initial dose of 50 mg/die to 93% of patients, and in total 336 discontinuations were observed for 22% of patients. Almost half of discontinuations occurred due to adverse reactions. During the observation period, 58% of patients had a dose increase of safinamide and 6% had a dose decrease.

Safinamide was safe and well tolerated, and no major or unexpected safety concerns were identified. During observation, 46% of patients experienced 1435 AEs and 27.7% experienced 685 ADRs. AEs were mainly mild. One third of events were nervous system disorders (14% dyskinesias) and 14% of AEs were psychiatric disorders. Only 29 (2%) AEs had definite relation with safinamide, 13% had probable relation and 23% had possible relation. For 69.5% of events no action was taken with respect to safinamide.
Dyskinesia, which was the most frequently AE reported in other studies[3,4], was also the most frequent event in the SYNAPSES study, although it occurred in a lower frequency in the SYNAPSES study (14% vs 31%). Other events occurred in less than 3% of patients in the SYNAPSES study included: fall (2.6%), headache (1.2%) and back pain (1.0%). No relevant frequency of cataract, constipation was reported. Hallucination, which could be related to other dopaminergic side effects, was observed in 2.9% of the overall sample.

No relevant differences emerged in the safinamide initial daily dose by younger and older patients: at the start of treatment, the majority of patients (93% in patients aged ≤ 75 and 93% in patients aged > 75) were administered with a daily dose of 50 mg. During study, 21% and 23% of evaluable patients aged ≤ 75 and > 75 respectively, permanently discontinued safinamide.

The proportions of patients experiencing AE were similar in the population of patients aged > 75 (47%) when compared to patients aged ≤ 75 (45%). No relevant differences emerged in severity or in action taken between the two age groups (patients aged ≤ 75 and > 75). Dyskinesia was still the most frequent AE in elderly patients (9.5%), with a lower frequency than the overall sample (13.7%). On the other hand, other AEs had higher frequency than the overall sample, namely hallucinations (5.1% in elderly patients vs 2.9% in overall sample), fall (3.5% vs 2.6%) and somnolence (2.2% vs 1.2%). Both younger and older patients had similar safinamide treatment patterns, hence the difference in frequency of adverse events does not seem related to a different safinamide dose according to age.

The safinamide initial daily dose was 50-mg daily in 94% of patients with relevant comorbidities and in 90% of patients without relevant comorbidities. No test was performed to assess significance; however, it seems reasonable to interpret this as if a higher dosage could be administered in less fragile patients (i.e. in patients without relevant comorbidities). No relevant difference was observed regarding the rate of safinamide discontinuation according to the presence or absence of concomitant conditions.

A higher occurrence of AEs was observed in patients with comorbidities (49% and 38% of patients with and without relevant comorbidities, respectively). Dyskinesia was, again, the most frequent AE in the subgroup of patients with comorbidities (12.3%), with a similar frequency as the overall sample. The distribution of the occurrence of the other AEs was quite similar in the subgroup of patients with comorbidities and the overall sample.

Finally, dyskinesia was the most frequent AE in the subgroup of patients with psychiatric conditions too (15.6%), with a slightly higher frequency than in the overall sample (13.7%). Patients with psychiatric comorbidities also showed a higher occurrence of hallucinations (4.1% plus 1.5% visual hallucinations) and falls (3.4% vs 2.6% in the overall sample). On the other hand, no relevant difference emerged in safinamide initial daily dose by patients with or without psychiatric conditions. No relevant differences as for severity and action taken for adverse events were observed in patients with or without psychiatric conditions.

A different frequency of SAEs was observed according to age and comorbidities. In particular, 13.6% of SAEs in patients aged > 75 vs 7.7% in those agred ≤ 75. Patients aged > 75 had more SAEs not related to safinamide (85%) than patients aged ≤75 (69%). Moreover, 11% and 4.6% of patients with and without relevant comorbidities, respectively, had at least one SAE. This is an expected phenomenon given that elderly patients and patients with other conditions could experience more clinical events. Occurrence of SAEs in patients with and without psychiatric conditions was similar (10% and 8.4%, respectively). The most frequent SAE experienced by psychiatric patients was dyskinesia (0.8% vs 0.3% of the overall sample). In the other subgroups, lung infections were the most common SAE.

On the other hand, ADR did not occur more frequently in older patients when compared with younger patients (26.1% in patients aged > 75 vs 28.3% in patients aged ≤ 75), nor according to the presence of comorbidities. ADR occurred in a slightly higher frequency in patients with psychiatric conditions (31.0%) vs patients without (25.3%).

The SYNAPSES study also included 17% of patients with safinamide non-appropriate use (and only one case was declared as an off-label use by investigators): more than half of such patients were administered safinamide without fluctuations at treatment start. These data were checked during data cleaning procedures, so they were confirmed by clinicians. A non-structured

interview was conducted in order to clarify this phenomenon and in most of cases clinical judgement was to start the drug slightly before the occurrence of fluctuations. Another non-appropriate use of safinamide was a starting dose other than 50 mg/daily. Its impact on safety was evaluated and the occurrence of AEs was 10% lower in patients with inappropriate use.

11.2. Limitations

This observational study allowed for information on the safinamide safety and pattern of use in clinical practice during one year in the first post-commercialization phase of the product. The patients included constituted a convenience sample of all those who were administered safinamide during the study period because no random procedure was applied in site and patient selection. In order to minimize any selection bias, consecutive enrolment was requested by protocol.

Concerning the collection of adverse events, there was a theoretical risk of underestimation of AEs, due to the time between one study visit and the next, mainly for the retrospective observation period. The risk was considered to be small during study planning, but finally 50% of patients had a partially retrospective observation period. However, the Investigators were trained regarding the importance of such a collection and, as shown in the sensitivity analyses chapter, no relevant difference was observed when considering the frequency of AEs or SAEs in retrospective or prospective patients.

At the same time, a risk of overestimation was also identified due to the fact that clinicians were observed during their clinical practice and this might have changed their behavior, simply because they participated in the study (Hawthorne effect). Despite this potential effect, a lower portion of AEs was observed than in previous published clinical trials on safinamide.

Finally, the target sample size was considered to be achievable during the enrolment period on the basis of preliminary feasibility considerations. The number of patients included in the subgroups of interest, namely those aged > 75 and those having relevant concomitant conditions (such as psychiatric concomitant conditions), was not set a priori in order not to alter enrolment strategies and in order to include a wide population representative of real-life setting. It depended on clinical practice and it was informative of clinician judgement. Finally, the achieved absolute sample sizes for the subgroups of interest were not irrelevant and allowed for robust estimates.

11.3. Interpretation

The current report presents the results of a retrospective-prospective cohort DUS in Europe. During the initial marketing authorization procedure, the European Medicines Agency (EMA) recommended that Zambon provide additional real world data on safinamide given the uncertainties regarding categories of patients not well represented in clinical trials, namely patients aged > 75, with comorbidities, and those with concomitant psychiatric conditions.
Safinamide confirmed its safety profile, and no new events emerged. The SYNAPSES study was not aimed at assessing any increased incidence of side effects relating to dyskinesia versus other treatments, because only patients undergoing safinamide were enrolled. However, a comparison is possible with available literature data.

The findings of the SYNAPSES study confirm the results obtained during the development phases for the 50 mg/day or 100 mg/day doses: the majority of AEs such as dizziness, nausea,

nasopharingitis, headache, somnolence, arthralgia, and urinary tract infections were non-serious, mild to moderate in intensity, and they were completely resolved. Adverse events reported by > 5% of subjects included dyskinesia, Parkinson's disease (worsening), cataract, back pain, headache, hypertension[10].

In general, a lower occurrence of AEs was found in the SYNAPSES study than the one observed in clinical trials. This could be due to a possible under-reporting both from the patient and the clinician. However, in order to minimize this risk, site monitoring visits were performed in order to verify that all data were consistent with source data. Moreover, a final safety reconciliation was performed with the Sponsor's safety database. A recall bias is common when patients are under observation but, again, this could have led to a higher frequency of AEs.

Although not evident in the clinical data, retinal deterioration is considered an important potential risk in patients with Parkinson's disease treated with safinamide. During the SYNAPSES study, a limited incidence of eye disorders (3%) was observed, and these events were not serious (among eye disorders, two glaucomas and one cataract were observed).

The most frequent reported AE in the SYNAPSES study was dyskinesia, which was also found to be the most frequent AE during clinical trials [3, 4, 9, 10,] , although at different frequencies. Dyskinesia is reported as the most common side effect in mid- to late-stage Parkinson's disease patients treated with levodopa alone or in combination with other dopaminergic medicines (i.e. medications that increase the level and promote the action of dopamine)[11].

At the time of study planning, limited information about the benefits of safinamide was available for patients older than 75, with psychiatric illnesses, specifically psychosis, bipolar disorder or severe depression, or with other relevant comorbidities. The SYNAPSES study allowed to focus the observation on this specific population in order to increase knowledge about the drug. Elderly patients have similar safinamide tolerability as patients with comorbidity. This could be probably due to the fact that age and comorbidity are often stricly related. Psychiatric concomitant condition was not so closely related to age or other comorbidities, but again safinamide was found to be well tolerated.

11.4. Generalisability

In each participating site, patients were consecutively enrolled. These results reflect the clinical practice of the participant sites in the period of data collection for the study, which was the first years after safinamide commercialization.
Moreover, selection criteria in the study were wide, as this study was planned as a drug-utilization study. To be precise, no constraints regarding disease stage or duration were foreseen by the study protocol. Therefore the whole target population of the SYNAPSES study consisted of patients exposed to safinamide; even inappropriate use was accepted and patients were included in the study. The only exception was Germany, because this was not compliant with the local authorities' request.
Due to the availability of the drug distribution and the site authorization process, the final number of participating sites and enrolled patients was not uniformly distributed among countries. Most of patients were recluted from Italy and Spain. Patients were followed-up at three timepoints in the year with 85-88% of patients evaluable at follow-up visits. A different practice in follow-up visits as per routine clinical practice was observed in UK. Therefore generalization of results should take these local different distributions into account.

12. Other information

None.

13. Conclusion

The management of motor complications in Parkinson's Disease remains a significant challenge in which all available pharmacologic options involve a risk of inducing or exacerbating dyskinesias. The SYNAPSES study, conducted in a real word setting in six European countries, confirms the good safety profile of safinamide even in special groups of patients, namely elderly patients, patients with comorbidities and patients with psychiatric conditions.
Neither age, comorbidities, nor psychiatric conditions seem to have any relevant effect on its safety profile.
In conclusion, the SYNAPSES study provided new real-world evidence with important information for routine clinical practice management regarding safinamide tolerability.

14. References

1 Keus SHJ, Munneke M, Graziano M, et al. European Physiotherapy Guideline for Parkinson's Disease. 2014; KNGF/ParkinsonNet, the Netherlands.

2 Xadago® Summary Of Product Characteristics. https://www.ema.europa.eu/en/documents/product-information/xadago-epar-product-information_en.pdf

3 Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D, Stocchi F, Lucini V, Giuliani R, Forrest E, Rice P, Anand R; Study 016 Investigators. Randomized trial of Safinamide add-on to L-dopa in Parkinson's disease with motor fluctuations. Mov Disord. 2014;29(2):229-37.

4 Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt MH, Chirilineau D, Stocchi F, Lucini V, Giuliani R, Forrest E, Rice P, Anand R; Study 018 Investigators. Two-year, randomized, controlled study of safinamide as add-on to levodopa in mid to late Parkinson's disease. Mov Disord. 2014;29(10):1273-80.

5 Fahn S, Elton RL, UPDRS Program Members. Unified Parkinson's disease rating scale. In: Fahn S, Marsden CD, Goldstein M, Calne DB, editors. Recent developments in Parkinson's disease, Vol. 2. Florham Park, NJ: Macmillan Healthcare Information; 1987. p 153–163, 293–304.

6 Ramaker C, Marinus J, Stiggelbout AM, van Hilten BJ. Systematic evaluation of rating scales for impairment and disability in Parkinson's disease. Mov Disord 2002;17:867–876.

7 Rosa K, Fu M, Gilles L, Cerri K, Peeters M, Bubb J, Scott J. Validation of the Fatigue Severity Scale in chronic hepatitis C. Health Qual Life Outcomes. 2014 Jun 11;12:90..

8 Dixon, W.J., Massey, F.J. Introduction to Statistical Analysis. 4th Edition McGraw-Hill (1983) pp. 105-107.

[9] Stocchi F, Torti M. Adjuvant therapies for Parkinson's disease: critical evaluation of safinamide. Drug Des Devel Ther. 2016 Feb 5;10:609-18

[10] Schapira AH, Fox SH, Hauser RA, Jankovic J, Jost WH, Kenney C, Kulisevsky J, Pahwa R, Poewe W, Anand R. Assessment of Safety and Efficacy of Safinamide as a Levodopa Adjunct in Patients With Parkinson Disease and Motor Fluctuations: A Randomized Clinical Trial. JAMA Neurol. 2017;74:216-224.

[11] Warren Olanow C, Kieburtz K, Rascol O, Poewe W, Schapira AH, Emre M, Nissinen H, Leinonen M, Stocchi F; Stalevo Reduction in Dyskinesia Evaluation in Parkinson's Disease (STRIDE-PD) Investigators. Factors predictive of the development of Levodopa-induced dyskinesia and wearing-off in Parkinson's disease. Mov Disord. 2013;28(8):1064–1071. doi: 10.1002/mds.25364

Appendices
Annex 1. List of stand-alone documents

Number	Document reference number	Date	Title
1 *Study Protocol*	1.2	*17/02/2016*	Observational Study Protocol
2 *Study Protocol amendement for Germany*	1.2	*17/02/2016*	Observational Study Protocol *Amended version for German sites according to BfArM's request of 12 July 2016*
3 *Layout of eCRF*	1.1	*07/12/2016*	LAYOUT OF electronic CASE REPORT FORM
4 *UPDRS Questionnaire*			UPDRS
5 *Statistical Analysis Plan*	1.9	*28/06/2019*	STATISTICAL ANALYSIS PLAN For Final Statistical Report
6 *Final Statistical Report*	1.2	*06/02/2020*	FINAL STATISTICAL REPORT
7 Xadago SmPC			SUMMARY OF PRODUCT CHARACTERISTICS
8 List of EC			List of Ethics committees which evaluated the study

Annex 2. Additional information

Annex 2.1 Statistical tables set

Table A1. Details on other psychiatric conditions

Other Psychiatric condition	Treated N	Not treated N	Total patients N
DEPRESSION	50	18	68
MILD DEPRESSION	28	12	40
APATHY	7	26	33
MINOR DEPRESSION	25	5	30
HALLUCINATIONS	20	8	28
INSOMNIA	24	0	24
IMPULSE CONTROL DISORDER	5	17	22
DEPRESSIVE SYMPTOMS	10	8	18
BEHAVIOUR DISORDER	5	4	9
DYSTHYMIA	9	0	9
VISUAL HALLUCINATIONS	3	6	9
DEMENTIA	5	2	7
MOOD SWING	4	3	7
ADJUSTMENT DISORDER	4	2	6
COGNITIVE IMPAIRMENT	3	1	4
DEPRESSION (NOT MAJOR)	2	2	4
DEPRESSIVE EPISODE	3	1	4
PANIC ATTACKS	4	0	4
MILD COGNITIVE IMPAIRMENT	3	0	3
COMPULSIVE BEHAVIOUR	0	2	2
DEPRESSION SYMPTOMS	1	1	2
OBSESSIVE COMPULSIVE DISORDER	1	1	2
REACTIVE DEPRESSION	1	1	2
AGITATION	0	1	1
AGRESSION	0	1	1
ANXIETY DISORDER	0	1	1
ANXIETY SYNDROME	1	0	1
ANXIODEPRESSION	1	0	1
ATTENTION DISORDERS	0	1	1

Other Psychiatric condition	Treated N	Not treated N	Total patients N
BEGINNING DEMENTIA	1	0	1
BINGE EATING	0	1	1
CLAUSTROPHOBIA	0	1	1
CONDITION AFTER IMPULS CONTROL DISORDER	0	1	1
DELIRIUM	1	0	1
DEPRESSIVE SYNDROME	1	0	1
DISINHIBITION	0	1	1
DISTURBANCE TO DEMENTIA	0	1	1
DOPAMINE DYSREGULATION SYNDROME	0	1	1
EATING ANXIETY	0	1	1
ENCEPHALOPATHY	0	1	1
EPISODIC DEPRESSION (NOT MAJOR)	1	0	1
EX-ALCOHOLIC	1	0	1
FEAR	1	0	1
GAMBLING	0	1	1
HISTRIONIC PERSONALITY DISORDER	0	1	1
HYPERSEXUALITY	0	1	1
HYPOTHYMIA	0	1	1
IMPULSE CONTROL (GAMBLING) DISORDER	0	1	1
IMPULSE DISORDER	0	1	1
IMPULSE DISTURB	1	0	1
IMPULSIVE BEHAVIOUR DISORDER	0	1	1
INFANT BRAIN DAMAGE	0	1	1
IRRITABILITY	0	1	1
LUDOPATHY	0	1	1
MILD ANXIETY	1	0	1
MILD COMPULSIVE SHOPPING	0	1	1
MILD DEPRESSIVE EPISODE	1	0	1
MILD HALLUCINATIONS	0	1	1
MINOR DEPRESSION RECURRENT	1	0	1
MINOR DEPRESSIVE SYMPTOMS	0	1	1
MODERATE DEPRESSIVE EPISODE	1	0	1
MOOD DISORDER	0	1	1
ORGANIC AFFECTIVE DISORDER	1	0	1
ORGANIC DEPRESSION	1	0	1
PARKINSON DISEASE DEMENTIA	1	0	1

Other Psychiatric condition	Treated N	Not treated N	Total patients N
PATHOLOGICAL JEALOUSY	1	0	1
PSYCHOGENIC GAIT DISORDER	0	1	1
RECURRENT DEPRESSIVE DISORDER	1	0	1
RECURRENT DEPRESSIVE EPISODES	0	1	1
RECURRENT HALLUCINATIONS	0	1	1
RECURRENT MINOR DEPRESSION	0	1	1
REMOTE ANXIOUS DEPRESSIVE STATE	0	1	1
SEXUAL IDENTIFICATION DISORDER	0	1	1
SLIGHT DEPRESSION, NO CRITERIA FOR MAJOR DEPRESSION	0	1	1
SOMATIZATION DISORDER WITH RECURRENT ATYPICAL CHEST PAIN, DYSPNEA, AND THORACOLUMBAR PAIN	1	0	1
SOMATOFORM PAIN DISORDER	1	0	1
SPORADIC SLIGHT VISUAL HALLUCINATIONS	0	1	1
STABLE DEPRESSIVE EPISODES	1	0	1
STATUS AFTER DELIRIA	0	1	1
VISUAL AND AUDITORY HALLUCINATIONS	0	1	1

Table A2 Treatments for any other medical condition received during observation

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
Ace Inhibitors / Dihydropyridine Derivatives	Any	1 (0.1%)
	AMLODIPINE~RAMIPRIL	1 (0.1%)
Ace Inhibitors And Calcium Channel Blockers	Any	4 (0.3%)
	AMLODIPINE BESILATE~PERINDOPRIL ARGININE	4 (0.3%)
Ace Inhibitors And Diuretics	Any	16 (1.0%)
	DELAPRIL~INDAPAMIDE	1 (0.1%)
	HYDROCHLOROTHIAZIDE~LISINOPRIL	3 (0.2%)
	HYDROCHLOROTHIAZIDE~MOEXIPRIL HYDROCHLORIDE	1 (0.1%)
	HYDROCHLOROTHIAZIDE~RAMIPRIL	2 (0.1%)
	INDAPAMIDE~PERINDOPRIL ERBUMINE	4 (0.3%)
	PERINDOPRIL	5 (0.3%)
Ace Inhibitors, Other Combinations	Any	1 (0.1%)
	AMLODIPINE BESILATE~INDAPAMIDE~PERINDOPRIL ARGININE	1 (0.1%)
Ace Inhibitors, Plain	Any	176 (11.3%)
	CAPTOPRIL	4 (0.3%)
	DELAPRIL	1 (0.1%)
	ENALAPRIL MALEATE	46 (3.0%)
	ENALAPRIL MALEATE~HYDROCHLOROTHIAZIDE	7 (0.4%)
	ENALAPRIL MALEATE~LERCANIDIPINE HYDROCHLORIDE	2 (0.1%)
	HYDROCHLOROTHIAZIDE~LISINOPRIL	3 (0.2%)
	HYDROCHLOROTHIAZIDE~QUINAPRIL HYDROCHLORIDE	1 (0.1%)
	HYDROCHLOROTHIAZIDE~RAMIPRIL	1 (0.1%)
	HYDROCHLOROTHIAZIDE~ZOFENOPRIL CALCIUM	1 (0.1%)
	LISINOPRIL	26 (1.7%)
	LISINOPRIL DIHYDRATE	1 (0.1%)
	PERINDOPRIL ARGININE	8 (0.5%)
	PERINDOPRIL ERBUMINE	2 (0.1%)
	QUINAPRIL HYDROCHLORIDE	1 (0.1%)
	RAMIPRIL	68 (4.4%)
	ZOFENOPRIL	2 (0.1%)
	ZOFENOPRIL CALCIUM	4 (0.3%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
Acetic Acid Derivatives And Related Substances	Any	11 (0.7%)
	ACECLOFENAC	1 (0.1%)
	DICLOFENAC POTASSIUM	1 (0.1%)
	DICLOFENAC SODIUM	6 (0.4%)
	ETODOLAC	1 (0.1%)
	INDOMETACIN	2 (0.1%)
	KETOROLAC TROMETHAMINE	1 (0.1%)
Adrenergic And Dopaminergic Agents	Any	15 (1.0%)
	ETILEFRINE HYDROCHLORIDE	3 (0.2%)
	MESALAZINE	3 (0.2%)
	METHOCARBAMOL	1 (0.1%)
	MIDODRINE HYDROCHLORIDE	8 (0.5%)
Adrenergics In Combination With Anticholinergics	Any	3 (0.2%)
	FENOTEROL HYDROBROMIDE~IPRATROPIUM BROMIDE	3 (0.2%)
Adrenergics In Combination With Corticosteroids Or Other Drugs, Excl. Anticholinergics	Any	23 (1.5%)
	BECLOMETASONE DIPROPIONATE~FORMOTEROL FUMARATE	3 (0.2%)
	BUDESONIDE~FORMOTEROL FUMARATE	8 (0.5%)
	FLUTICASONE FUROATE~VILANTEROL TRIFENATATE	1 (0.1%)
	FLUTICASONE PROPIONATE~FORMOTEROL FUMARATE	1 (0.1%)
	FLUTICASONE PROPIONATE~SALMETEROL XINAFOATE	10 (0.6%)
Adrenergics In Combinations With Anticholinergics Incl. Triple Combinations With Corticosteroids	Any	1 (0.1%)
	ACLIDINIUM BROMIDE~FORMOTEROL FUMARATE	1 (0.1%)
Aldosterone Antagonists	Any	23 (1.5%)
	CANRENOIC ACID	3 (0.2%)
	FUROSEMIDE~SPIRONOLACTONE	2 (0.1%)
	POTASSIUM CANRENOATE	1 (0.1%)
	SPIRONOLACTONE	17 (1.1%)
Alkaloids	Any	1 (0.1%)
	COLCHICINE	1 (0.1%)
Alpha And Beta Blocking Agents	Any	13 (0.8%)
	CARVEDILOL	13 (0.8%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
Alpha-Adrenoreceptor Antagonists	Any	92 (5.9%)
	ALFUZOSIN	4 (0.3%)
	ALFUZOSIN HYDROCHLORIDE	6 (0.4%)
	DOXAZOSIN	2 (0.1%)
	DOXAZOSIN MESILATE	11 (0.7%)
	DUTASTERIDE~TAMSULOSIN HYDROCHLORIDE	17 (1.1%)
	SILODOSIN	19 (1.2%)
	TAMSULOSIN HYDROCHLORIDE	29 (1.9%)
	TERAZOSIN HYDROCHLORIDE	5 (0.3%)
	URAPIDIL	1 (0.1%)
Alpha-Adrenoreceptor Antagonists / Testosterone-5-Alpha Reductase Inhibitors	Any	5 (0.3%)
	DUTASTERIDE~TAMSULOSIN	5 (0.3%)
Alpha-Adrenoreceptor Inhibitors	Any	40 (2.6%)
	TAMSULOSIN HYDROCHLORIDE	40 (2.6%)
Amantadine	Any	8 (0.5%)
	AMANTADINE	7 (0.4%)
	AMANTADINE SULFATE	1 (0.1%)
Amides	Any	8 (0.5%)
	BUPIVACAINE	1 (0.1%)
	LIDOCAINE	7 (0.4%)
Amino Acids	Any	1 (0.1%)
	LYSINE ACETATE	1 (0.1%)
Aminoalkyl Ethers	Any	1 (0.1%)
	DIMENHYDRINATE	1 (0.1%)
Aminoquinolines	Any	4 (0.3%)
	CHLOROQUINE PHOSPHATE	1 (0.1%)
	HYDROXYCHLOROQUINE SULFATE	3 (0.2%)
Aminosalicylic Acid And Similar Agents	Any	2 (0.1%)
	MESALAZINE	1 (0.1%)
	SULFASALAZINE	1 (0.1%)
Angiotensin Ii Antagonists / Dihydropyridine Derivatives	Any	6 (0.4%)
	AMLODIPINE BESILATE~VALSARTAN	1 (0.1%)
	AMLODIPINE~OLMESARTAN	4 (0.3%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	OLMESARTAN MEDOXOMIL	1 (0.1%)
Angiotensin Ii Antagonists / Diuretics	Any	10 (0.6%)
	HYDROCHLOROTHIAZIDE~LOSARTAN POTASSIUM	5 (0.3%)
	HYDROCHLOROTHIAZIDE~TELMISARTAN	1 (0.1%)
	HYDROCHLOROTHIAZIDE~VALSARTAN	4 (0.3%)
Angiotensin Ii Antagonists And Calcium Channel Blockers	Any	6 (0.4%)
	AMLODIPINE BESILATE~OLMESARTAN MEDOXOMIL	6 (0.4%)
Angiotensin Ii Antagonists And Diuretics	Any	39 (2.5%)
	CANDESARTAN CILEXETIL	2 (0.1%)
	CANDESARTAN CILEXETIL~HYDROCHLOROTHIAZIDE	6 (0.4%)
	EPROSARTAN MESILATE	1 (0.1%)
	EPROSARTAN MESILATE~HYDROCHLOROTHIAZIDE	1 (0.1%)
	HYDROCHLOROTHIAZIDE~IRBESARTAN	9 (0.6%)
	HYDROCHLOROTHIAZIDE~LOSARTAN POTASSIUM	1 (0.1%)
	HYDROCHLOROTHIAZIDE~OLMESARTAN MEDOXOMIL	8 (0.5%)
	HYDROCHLOROTHIAZIDE~TELMISARTAN	6 (0.4%)
	HYDROCHLOROTHIAZIDE~VALSARTAN	5 (0.3%)
Angiotensin Ii Antagonists, Plain	Any	154 (9.9%)
	AMLODIPINE BESILATE~HYDROCHLOROTHIAZIDE~OLMESARTAN MEDOXOMIL	1 (0.1%)
	AMLODIPINE BESILATE~VALSARTAN	3 (0.2%)
	CANDESARTAN CILEXETIL	18 (1.2%)
	CANDESARTAN CILEXETIL~HYDROCHLOROTHIAZIDE	2 (0.1%)
	CANNABIDIOL	2 (0.1%)
	EPROSARTAN MESILATE	1 (0.1%)
	HYDROCHLOROTHIAZIDE~IRBESARTAN	3 (0.2%)
	HYDROCHLOROTHIAZIDE~LOSARTAN	1 (0.1%)
	HYDROCHLOROTHIAZIDE~TELMISARTAN	1 (0.1%)
	HYDROCHLOROTHIAZIDE~VALSARTAN	4 (0.3%)
	IMIDAPRIL HYDROCHLORIDE	2 (0.1%)
	IRBESARTAN	16 (1.0%)
	LACIDIPINE	7 (0.4%)
	LOSARTAN POTASSIUM	38 (2.4%)
	OLMESARTAN MEDOXOMIL	20 (1.3%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	TELMISARTAN	16 (1.0%)
	VALSARTAN	22 (1.4%)
Anilides	Any	81 (5.2%)
	CODEINE PHOSPHATE~PARACETAMOL	4 (0.3%)
	CODEINE~PARACETAMOL	1 (0.1%)
	DIHYDROCODEINE BITARTRATE~PARACETAMOL	1 (0.1%)
	ERGOTAMINE TATRATE~PARACETAMOL	1 (0.1%)
	PARACETAMOL	68 (4.4%)
	PARACETAMOL~TRAMADOL HYDROCHLORIDE	6 (0.4%)
Anti-Androgens	Any	1 (0.1%)
	BICALUTAMIDE	1 (0.1%)
Anti-Estrogens	Any	2 (0.1%)
	TAMOXIFEN	2 (0.1%)
Anti-Infectives And Antiseptics For Local Oral Treatment	Any	1 (0.1%)
	METRODINAZOLE	1 (0.1%)
Anti-Inflammatory Products For Vaginal Administration	Any	3 (0.2%)
	NAPROXEN	3 (0.2%)
Antiarrhythmics Class Ic	Any	17 (1.1%)
	FLECAINIDE ACETATE	15 (1.0%)
	PROPAFENONE HYDROCHLORIDE	2 (0.1%)
Antiarrhythmics, Class Iii	Any	6 (0.4%)
	AMIODARONE	2 (0.1%)
	AMIODARONE HYDROCHLORIDE	4 (0.3%)
Antibiotics	Any	15 (1.0%)
	ALTIZIDE~SPIRONOLACTONE	2 (0.1%)
	AMOXICILLIN	2 (0.1%)
	AMOXICILLIN SODIUM~CLAVULANATE POTASSIUM	1 (0.1%)
	AMOXICILLIN TRIHYDRATE~CLAVULANATE POTASSIUM	6 (0.4%)
	AMPICILLIN~SPIRONOLACTONE	1 (0.1%)
	RIFAXIMIN	2 (0.1%)
	UNKNOWN ANTIBIOTIC	1 (0.1%)
Anticholinergics	Any	20 (1.3%)
	ECHINACEA ANGUSTIFOLIA ROOT~SERENOA REPENS FRUIT~TROSPIUM CHLORIDE	1 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	GLYCOPYRRONIUM	1 (0.1%)
	GLYCOPYRRONIUM BROMIDE	3 (0.2%)
	IPRATROPIUM BROMIDE	2 (0.1%)
	IPRATROPIUM BROMIDE~SALBUTAMOL SULFATE	1 (0.1%)
	MEBEVERINE EMBONATE	2 (0.1%)
	OTILONIUM	1 (0.1%)
	OXYBUTYNIN	1 (0.1%)
	TIOTROPIUM BROMIDE	7 (0.4%)
	UMECLIDINIUM BROMIDE	1 (0.1%)
Anticholinesterases	Any	44 (2.8%)
	DONEPEZIL	6 (0.4%)
	DONEPEZIL HYDROCHLORIDE	1 (0.1%)
	PYRIDOSTIGMINE BROMIDE	3 (0.2%)
	RIVASTIGMINE	34 (2.2%)
Antidepressants	Any	181 (11.6%)
	AGOMELATINE	6 (0.4%)
	AMISULPRIDE	2 (0.1%)
	BUPROPION	1 (0.1%)
	BUPROPION HYDROCHLORIDE	15 (1.0%)
	MIANSERIN HYDROCHLORIDE	2 (0.1%)
	MIRTAZAPINE	85 (5.5%)
	REBOXETINE	1 (0.1%)
	REBOXETINE MESILATE	1 (0.1%)
	TIANEPTINE SODIUM	2 (0.1%)
	TRAZODONE HYDROCHLORIDE	62 (4.0%)
	VENLAFAXINE HYDROCHLORIDE	2 (0.1%)
	VORTIOXETINE	2 (0.1%)
	VORTIOXETINE HYDROBROMIDE	16 (1.0%)
Antidepressants (Tricyclic)	Any	41 (2.6%)
	AMITRIPTYLINE HYDROCHLORIDE	33 (2.1%)
	CLOMIPRAMINE HYDROCHLORIDE	4 (0.3%)
	DOXEPIN	1 (0.1%)
	DOXEPIN HYDROCHLORIDE	1 (0.1%)
	MAPROTILINE HYDROCHLORIDE	1 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	TRIMIPRAMINE MALEATE	1 (0.1%)
Antidepressants In Combination With Psycholeptics	Any	2 (0.1%)
	AMITRIPTYLINE HYDROCHLORIDE~PERPHENAZINE	1 (0.1%)
	PINEAL NOTTE	1 (0.1%)
Antidiabetic Drug	Any	3 (0.2%)
	DAPAGLIFLOZIN PROPANEDIOL MONOHYDRATE~METFORMIN HYDROCHLORIDE	1 (0.1%)
	LINAGLIPTIN~METFORMIN	1 (0.1%)
	METFORMIN HYDROCHLORIDE~VILDAGLIPTIN	1 (0.1%)
Antidiarrheal Microorganisms	Any	1 (0.1%)
	LACTOBACILLUS ACIDOPHILUS	1 (0.1%)
Antihistamines For Topical Use	Any	1 (0.1%)
	DEXCHLORPHENIRAMINE MALEATE	1 (0.1%)
Antihypertensive Agent	Any	1 (0.1%)
	ACETAZOLAMIDE	1 (0.1%)
Antiinfectives	Any	1 (0.1%)
	BENZOCAINE~CETYLPYRIDINIUM CHLORIDE	1 (0.1%)
Antiinfectives And Antiseptics For Local Oral Treatment	Any	1 (0.1%)
	NYSTATIN	1 (0.1%)
Antiinflammatory Agents, Non-Steroids	Any	13 (0.8%)
	ACECLOFENAC	1 (0.1%)
	DICLOFENAC RESINATE	2 (0.1%)
	DICLOFENAC SODIUM	10 (0.6%)
Antiinflammatory Preparations, Non-Steroids For Topical Use	Any	3 (0.2%)
	ACECLOFENAC	1 (0.1%)
	IBUPROFEN	1 (0.1%)
	KETOPROFEN	1 (0.1%)
Antipsychotics	Any	150 (9.6%)
	ASENAPINE MALEATE	2 (0.1%)
	CLOZAPINE	25 (1.6%)
	LITHIUM CARBONATE	1 (0.1%)
	OLANZAPINE	4 (0.3%)
	QUETIAPINE FUMARATE	122 (7.8%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
Antivertigo Preparations	Any	15 (1.0%)
	BETAHISTINE	3 (0.2%)
	BETAHISTINE HYDROCHLORIDE	11 (0.7%)
	CINNARIZINE	1 (0.1%)
Antivirals	Any	4 (0.3%)
	ACICLOVIR	4 (0.3%)
Anxiolytics	Any	16 (1.0%)
	ETHINYLESTRADIOL~ETHISTERONE	2 (0.1%)
	FLUPENTIXOL DIHYDROCHLORIDE~MELITRACEN HYDROCHLORIDE	1 (0.1%)
	ZOLPIDEM TARTRATE	11 (0.7%)
	ZOPICLONE	2 (0.1%)
Anxiolytics (Benzodiazepine Derivative)	Any	375 (24.1%)
	ALPRAZOLAM	51 (3.3%)
	BROMAZEPAM	36 (2.3%)
	BROMHEXINE HYDROCHLORIDE~CHLORPHENAMINE MALEATE~DEXTROMETHORPHAN HYDROBROMIDE~PHENYLPROPANOLAMINE HYDROCHLORIDE	1 (0.1%)
	BROTIZOLAM	3 (0.2%)
	CLOBAZAM	1 (0.1%)
	CLONAZEPAM	152 (9.8%)
	CLORAZEPATE DIPOTASSIUM	7 (0.4%)
	CLOTIAZEPAM	2 (0.1%)
	DELORAZEPAM	5 (0.3%)
	DIAZEPAM	13 (0.8%)
	DIAZEPAM~PYRIDOXINE HYDROCHLORIDE~THIAMINE HYDROCHLORIDE	1 (0.1%)
	DILTIAZEM	3 (0.2%)
	DILTIAZEM HYDROCHLORIDE	3 (0.2%)
	FLURAZEPAM HYDROCHLORIDE	1 (0.1%)
	HYDROXYZINE HYDROCHLORIDE	4 (0.3%)
	LORATADINE	1 (0.1%)
	LORAZEPAM	74 (4.7%)
	LORMETAZEPAM	34 (2.2%)
	MIDAZOLAM	2 (0.1%)
	PRAZEPAM	2 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	TRIAZOLAM	4 (0.3%)
	ZOLPIDEM TARTRATE	9 (0.6%)
	ZOPICLONE	7 (0.4%)
Appetite Stimulants	Any	1 (0.1%)
	CYPROHEPTADINE HYDROCHLORIDE	1 (0.1%)
Aromatase Inhibitors	Any	5 (0.3%)
	EXEMESTANE	1 (0.1%)
	LETROZOLE	4 (0.3%)
Barbiturates, Plain	Any	1 (0.1%)
	METHOHEXITAL	1 (0.1%)
Belladonna Alkaloids, Semisynthetic, Quaternary Ammonium Compounds	Any	1 (0.1%)
	HYOSCINE BUTYLBROMIDE	1 (0.1%)
Belladonna Alkaloids, Tertiary Amines	Any	1 (0.1%)
	ATROPINE	1 (0.1%)
Benzamides	Any	1 (0.1%)
	LEVOSULPIRIDE	1 (0.1%)
Benzimidazole Derivatives	Any	1 (0.1%)
	TIABENDAZOLE	1 (0.1%)
Benzodiazepine Derivatives	Any	4 (0.3%)
	CHLORDIAZEPOXIDE~CLIDINIUM BROMIDE	1 (0.1%)
	CLORAZEPATE DIPOTASSIUM	1 (0.1%)
	LORAZEPAM PIVALATE	1 (0.1%)
	OXAZEPAM	1 (0.1%)
Beta Blocking Agents	Any	13 (0.8%)
	BIMATOPROST~TIMOLOL MALEATE	5 (0.3%)
	BISOPROLOL	1 (0.1%)
	DORZOLAMIDE HYDROCHLORIDE~TIMOLOL MALEATE	4 (0.3%)
	TIMOLOL MALEATE	4 (0.3%)
Beta Blocking Agents, Non-Selective	Any	32 (2.1%)
	BENZALKONIUM CHLORIDE~TIMOLOL MALEATE	1 (0.1%)
	LATANOPROST~TIMOLOL MALEATE	1 (0.1%)
	PROPRANOLOL HYDROCHLORIDE	23 (1.5%)
	SOTALOL HYDROCHLORIDE	5 (0.3%)
	TIMOLOL MALEATE	2 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
Beta Blocking Agents, Selective	Any	209 (13.4%)
	ATENOLOL	23 (1.5%)
	ATENOLOL~CHLORTALIDONE	1 (0.1%)
	BISOPROLOL FUMARATE	59 (3.8%)
	BISOPROLOL FUMARATE~HYDROCHLOROTHIAZIDE	52 (3.3%)
	BISOPROLOL HEMIFUMARATE	7 (0.4%)
	HYDROCHLOROTHIAZIDE~NEBIVOLOL HYDROCHLORIDE	3 (0.2%)
	METOPROLOL SUCCINATE	9 (0.6%)
	METOPROLOL TARTRATE	26 (1.7%)
	NEBIVOLOL HYDROCHLORIDE	30 (1.9%)
Beta Blocking Agents, Selective, And Other Diuretics	Any	1 (0.1%)
	ATENOLOL~CHLORTALIDONE	1 (0.1%)
Beta Blocking Agents, Selective, And Thiazides	Any	6 (0.4%)
	BISOPROLOL FUMARATE~HYDROCHLOROTHIAZIDE	4 (0.3%)
	HYDROCHLOROTHIAZIDE~NEBIVOLOL HYDROCHLORIDE	2 (0.1%)
Biguanides	Any	97 (6.2%)
	CANAGLIFLOZIN HEMIHYDRATE~METFORMIN HYDROCHLORIDE	1 (0.1%)
	GLIBENCLAMIDE~PHENFORMIN HYDROCHLORIDE	1 (0.1%)
	LINAGLIPTIN~METFORMIN HYDROCHLORIDE	1 (0.1%)
	METFORMIN HYDROCHLORIDE	93 (6.0%)
	METFORMIN HYDROCHLORIDE~SITAGLIPTIN PHOSPHATE MONOHYDRATE	3 (0.2%)
	METFORMIN~SITAGLIPTIN	1 (0.1%)
Bile Acid Preparations	Any	1 (0.1%)
	URSODEOXYCHOLIC ACID	1 (0.1%)
Bile Acids And Derivatives	Any	4 (0.3%)
	URSODEOXYCHOLIC ACID	4 (0.3%)
Bisphosphonates	Any	23 (1.5%)
	ALENDRONATE SODIUM	5 (0.3%)
	ALENDRONATE SODIUM~COLECALCIFEROL	1 (0.1%)
	ALENDRONIC ACID	3 (0.2%)
	CLODRONATE DISODIUM	2 (0.1%)
	IBANDRONATE SODIUM	6 (0.4%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	IBRANDONATE	1 (0.1%)
	RISEDRONATE SODIUM	2 (0.1%)
	RISEDRONIC ACID	2 (0.1%)
	ZOLEDRONIC ACID	1 (0.1%)
Bisphosphonates, Combinations	Any	6 (0.4%)
	ALENDRONATE SODIUM~COLECALCIFEROL	6 (0.4%)
Butyrophenone Derivatives	Any	1 (0.1%)
	CYANOCOBALAMIN~PYRIDOXINE HYDROCHLORIDE~THIAMINE HYDROCHLORIDE	1 (0.1%)
Calcineurin Inhibitors	Any	3 (0.2%)
	TACROLIMUS	3 (0.2%)
Calcium	Any	4 (0.3%)
	CALCIUM CARBONATE	3 (0.2%)
	CALCIUM CARBONATE~COLECALCIFEROL	1 (0.1%)
Calcium Compounds	Any	25 (1.6%)
	ALENDRONATE SODIUM	1 (0.1%)
	CALCITRIOL	1 (0.1%)
	CALCIUM	2 (0.1%)
	CALCIUM CARBONATE~COLECALCIFEROL	8 (0.5%)
	CALCIUM GLUCONATE - CALCIUM SACCHARATE	12 (0.8%)
	CALCIUM PIDOLATE~COLECALCIFEROL	1 (0.1%)
Calcium, Combinations With Vitamin D And/Or Other Drugs	Any	19 (1.2%)
	CALCIUM CARBONATE~COLECALCIFEROL	18 (1.2%)
	CALCIUM~COLECALCIFEROL	1 (0.1%)
Carbapenems	Any	2 (0.1%)
	ERTAPENEM	1 (0.1%)
	MEROPENEM	1 (0.1%)
Carbonic Anhydrase Inhibitors	Any	6 (0.4%)
	BRINZOLAMIDE	4 (0.3%)
	DORZOLAMIDE HYDROCHLORIDE	2 (0.1%)
Centrally Acting Sympathomimetics	Any	2 (0.1%)
	MODAFINIL	2 (0.1%)
Colony Stimulating Factors	Any	1 (0.1%)
	FILGRASTIM	1 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
Combinations And Complexes Of Aluminium, Calcium And Magnesium Compounds	Any	2 (0.1%)
	ALMAX	1 (0.1%)
	DIMETICONE~MAGALDRATE	1 (0.1%)
Combinations Of Antineoplastic Agents	Any	1 (0.1%)
	CHLORAMBUCIL~OBINUTUZUMAB	1 (0.1%)
Combinations Of Oral Blood Glucose Lowering Drugs	Any	14 (0.9%)
	ALOGLIPTIN BENZOATE~METFORMIN HYDROCHLORIDE	1 (0.1%)
	GLIBENCLAMIDE~METFORMIN HYDROCHLORIDE	2 (0.1%)
	GLIBENCLAMIDE~PHENFORMIN HYDROCHLORIDE	2 (0.1%)
	METFORMIN HYDROCHLORIDE~SAXAGLIPTIN HYDROCHLORIDE	2 (0.1%)
	METFORMIN HYDROCHLORIDE~SITAGLIPTIN PHOSPHATE	4 (0.3%)
	METFORMIN HYDROCHLORIDE~VILDAGLIPTIN	3 (0.2%)
Combinations Of Penicillins, Incl. Beta-Lactamase Inhibitors	Any	6 (0.4%)
	AMPICILLIN SODIUM - SULBACTAM SODIUM	2 (0.1%)
	PIPERACILLIN SODIUM~TAZOBACTAM SODIUM	4 (0.3%)
Combinations Of Sulfonamides And Trimethoprim, Incl. Derivatives	Any	4 (0.3%)
	SULFAMETHOXAZOLE~TRIMETHOPRIM	4 (0.3%)
Combinations Of Vitamins	Any	1 (0.1%)
	FOLIC ACID~PYRIDOXINE HYDROCHLORIDE~THIAMINE HYDROCHLORIDE~VITAMIN B12 NOS	1 (0.1%)
Comt Inhibitors	Any	1 (0.1%)
	OPICAPONE	1 (0.1%)
Contact Laxatives	Any	9 (0.6%)
	BISACODYL	5 (0.3%)
	SODIUM PICOSULFATE	4 (0.3%)
Corticosteroids	Any	13 (0.8%)
	CICLESONIDE	1 (0.1%)
	DEFLAZACORT	1 (0.1%)
	HYDROCORTISONE	2 (0.1%)
	METHYLPREDNISOLONE	1 (0.1%)
	METHYLPREDNISOLONE ACEPONATE	1 (0.1%)
	MOMETASONE FUROATE	2 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	PREDNISONE	5 (0.3%)
Corticosteroids Acting Locally	Any	13 (0.8%)
	BECLOMETASONE	2 (0.1%)
	BECLOMETASONE DIPROPIONATE	3 (0.2%)
	BETAMETHASONE SODIUM PHOSPHATE	2 (0.1%)
	BETAMETHASONE VALERATE	1 (0.1%)
	BUDESONIDE	3 (0.2%)
	PREDNISOLONE	1 (0.1%)
	PREDNISONE	1 (0.1%)
Corticosteroids And Antiinfectives In Combination	Any	2 (0.1%)
	DEXAMETHASONE~TOBRAMYCIN	2 (0.1%)
Corticosteroids For Local Oral Treatment	Any	1 (0.1%)
	DEXAMETHASONE	1 (0.1%)
Corticosteroids, Potent (Group Iii)	Any	5 (0.3%)
	BECLOMETASONE DIPROPIONATE	1 (0.1%)
	BETAMETHASONE DIPROPIONATE~SALICYLIC ACID	1 (0.1%)
	FLUTICASONE FUROATE~VILANTEROL TRIFENATATE	1 (0.1%)
	FLUTICASONE PROPIONATE	1 (0.1%)
	MOMETASONE FUROATE	1 (0.1%)
Coxibs	Any	4 (0.3%)
	ETORICOXIB	4 (0.3%)
Diazepines, Oxazepines, Thiazepines And Oxepines	Any	2 (0.1%)
	OLANZAPINE	2 (0.1%)
Dietary Integrator	Any	1 (0.1%)
	MEDIFLUSS	1 (0.1%)
Dietary Supplement	Any	31 (2.0%)
	PINUS MASSONIANA, CROCUS SATIVUS AND SERENOA REPENS	1 (0.1%)
	BROMELAIN~MSM~HYALURONIC ACID~BOSWELLIA	1 (0.1%)
	CAFFEINE~CARBOHYDRATES NOS FATS NOS~ FIBRE DIETARY~MINERALS NOS~PROTEINS NOS~VITAMINS NOS	4 (0.3%)
	CIANOKOBALAMIN~FOLIC ACID ~URIDINE THRIPHOSPHATE SODIUM	1 (0.1%)
	CO Q10~ VITAMIN E~SELENIUM~ SUNFLOWER OIL	1 (0.1%)
	COMPLAN ORAL POWDER SACHET	1 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	DERMATAN SULFATE	1 (0.1%)
	DRY EXTRACT FROM RHAMNUS PURSHIANA DC AND RHAMNUS FRANGULA L.	1 (0.1%)
	FERROUS GLYCINE SULFATE	2 (0.1%)
	FERROUS SULFATE	1 (0.1%)
	FIBER	1 (0.1%)
	GLUCOSAMINE HYDROCHLORIDE~ CONDROITIN SULFATE ~BIO CURCUMIN BCM-95	1 (0.1%)
	IRON SULFATE~VITAMIN C~VITAMIN B6~VITAMIN B12~ FOLIC ACID	1 (0.1%)
	L-METIONIN ~CRANBERRY	1 (0.1%)
	LEVOTHYROXINE SODIUM~LIOTHYRONINE SODIUM	2 (0.1%)
	MALTODEXTRIN	1 (0.1%)
	OMEGA-3 TRIGLYCERIDES	2 (0.1%)
	PLANTAGOOVATA	1 (0.1%)
	POLYURETHANE	1 (0.1%)
	PRUNUS AFRICANA	2 (0.1%)
	PSYLLIUM FIBER	1 (0.1%)
	RED RICE YEAST	1 (0.1%)
	RED YEAST RICE (MONASCUS PURPUREUS)	1 (0.1%)
	UBIDECARENONE	2 (0.1%)
	VITAMIN A, D, E AND K	1 (0.1%)
Digitalis Glycosides	Any	7 (0.4%)
	BETA-ACETYLDIGOXIN	6 (0.4%)
	DIGITOXIN	1 (0.1%)
Dihydropyridine Derivatives	Any	97 (6.2%)
	AMLODIPINE	10 (0.6%)
	AMLODIPINE BESILATE	36 (2.3%)
	AMLODIPINE BESILATE~BISOPROLOL FUMARATE	1 (0.1%)
	AMLODIPINE BESILATE~HYDROCHLOROTHIAZIDE~OLMESARTAN MEDOXOMIL	1 (0.1%)
	AMLODIPINE BESILATE~OLMESARTAN MEDOXOMIL	2 (0.1%)
	BARNIDIPINE	1 (0.1%)
	BARNIDIPINE HYDROCHLORIDE	2 (0.1%)
	CALCIUM CARBONATE	1 (0.1%)
	FEBUXOSTAT	1 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	FELODIPINE	4 (0.3%)
	LACIDIPINE	3 (0.2%)
	LERCANIDIPINE	12 (0.8%)
	LERCANIDIPINE HYDROCHLORIDE	9 (0.6%)
	MANIDIPINE	1 (0.1%)
	MANIDIPINE HYDROCHLORIDE	3 (0.2%)
	MORPHINE HYDROCHLORIDE	3 (0.2%)
	NIFEDIPINE	8 (0.5%)
	VERAPAMIL HYDROCHLORIDE	2 (0.1%)
Dipeptidyl Peptidase 4 (Dpp-4) Inhibitors	Any	9 (0.6%)
	LINAGLIPTIN	5 (0.3%)
	SAXAGLIPTIN HYDROCHLORIDE	1 (0.1%)
	SITAGLIPTIN	1 (0.1%)
	SITAGLIPTINA	1 (0.1%)
	VILDAGLIPTIN	1 (0.1%)
Direct Factor Xa Inhibitors	Any	50 (3.2%)
	APIXABAN	28 (1.8%)
	EDOXABAN TOSILATE	1 (0.1%)
	RIVAROXABAN	21 (1.3%)
Direct Thrombin Inhibitors	Any	6 (0.4%)
	DABIGATRAN ETEXILATE MESILATE	6 (0.4%)
Dopamine Agonist	Any	5 (0.3%)
	APOMORPHINE	1 (0.1%)
	PRAMIPEXOLE DIHYDROCHLORIDE	1 (0.1%)
	ROPINIROLE HYDROCHLORIDE	1 (0.1%)
	ROTIGOTINE	2 (0.1%)
Drugs For Treatment Of Hyperkalemia And Hyperphosphatemia	Any	2 (0.1%)
	CALCIUM POLYSTYRENE SULFONATE	1 (0.1%)
	SODIUM POLYSTYRENE SULFONATE	1 (0.1%)
Drugs For Urinary Frequency And Incontinence	Any	80 (5.1%)
	DARIFENACIN HYDROBROMIDE	1 (0.1%)
	FESOTERODINE	1 (0.1%)
	FESOTERODINE FUMARATE	13 (0.8%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	MIRABEGRON	25 (1.6%)
	OXYBUTYNIN	3 (0.2%)
	OXYBUTYNIN HYDROCHLORIDE	5 (0.3%)
	PROPIVERINE HYDROCHLORIDE	2 (0.1%)
	SOLIFENACIN SUCCINATE	25 (1.6%)
	SOLIFENACIN SUCCINATE~TAMSULOSIN HYDROCHLORIDE	6 (0.4%)
	TOLTERODINE L-TARTRATE	5 (0.3%)
	TROSPIUM CHLORIDE	3 (0.2%)
Drugs Used In Alcohol Dependence	Any	1 (0.1%)
	DISULFIRAM	1 (0.1%)
Drugs Used In Erectile Dysfunction	Any	8 (0.5%)
	LATANOPROST	1 (0.1%)
	SILDENAFIL	3 (0.2%)
	SILDENAFIL CITRATE	1 (0.1%)
	TADALAFIL	4 (0.3%)
Drugs Used In Opioid Dependence	Any	1 (0.1%)
	BUPRENORPHINE	1 (0.1%)
Electrolyte Solutions	Any	1 (0.1%)
	POTASSIUM CHLORIDE	1 (0.1%)
Enzyme Preparations	Any	4 (0.3%)
	PANCREATIN	4 (0.3%)
Ergot Alkaloids	Any	1 (0.1%)
	ERGOTAMINE TARTRATE	1 (0.1%)
Estrogen	Any	2 (0.1%)
	PROMESTRIENE	2 (0.1%)
Expectorants	Any	2 (0.1%)
	CINEOLE	1 (0.1%)
	POTASSIUM IODIDE	1 (0.1%)
Fatty Acid Derivatives	Any	8 (0.5%)
	VALPROATE MAGNESIUM	1 (0.1%)
	VALPROATE SODIUM	7 (0.4%)
Fibrates	Any	6 (0.4%)
	FENOFIBRATE	5 (0.3%)
	GEMFIBROZIL	1 (0.1%)
First Generation Cephalosporins	Any	2 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	CEFAZOLIN	2 (0.1%)
Flavonoids	Any	2 (0.1%)
	BIOFLAVONOIDS~DIOSMIN~HESPERIDIN	2 (0.1%)
Fluoroquinolones	Any	14 (0.9%)
	CIPROFLOXACIN (ANTIBIOTIC)	8 (0.5%)
	GLUCOSE - LEVOFLOXACIN	3 (0.2%)
	LEVOFLOXACIN	2 (0.1%)
	MOXIFLOXACIN	2 (0.1%)
Folic Acid Analogues	Any	2 (0.1%)
	METHOTREXATE	2 (0.1%)
Folic Acid And Derivatives	Any	38 (2.4%)
	CALCIUM MEFOLINATE	1 (0.1%)
	CYANOCOBALAMIN~FOLIC ACID	1 (0.1%)
	FOLIC ACID	36 (2.3%)
Glucocorticoids	Any	13 (0.8%)
	BUDESONIDE	1 (0.1%)
	CORTISONE ACETATE	2 (0.1%)
	DEXAMETHASONE	1 (0.1%)
	FLUTICASONE FUROATE	1 (0.1%)
	METHYLPREDNISOLONE	4 (0.3%)
	METHYLPREDNISOLONE ACETATE	1 (0.1%)
	PREDNISONE	3 (0.2%)
Gonadotropin-Releasing Hormone Analogues	Any	1 (0.1%)
	LEUPRORELIN	1 (0.1%)
H2-Receptor Antagonists	Any	8 (0.5%)
	FAMOTIDINE	1 (0.1%)
	RANITIDINE HYDROCHLORIDE	7 (0.4%)
H2-Receptors Inhibitors	Any	4 (0.3%)
	RANITIDINE	4 (0.3%)
Heparin Group	Any	20 (1.3%)
	BEMIPARIN SODIUM	3 (0.2%)
	ENOXAPARIN	2 (0.1%)
	ENOXAPARIN SODIUM	14 (0.9%)
	HEPARIN CALCIUM	1 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	PARNAPARIN SODIUM	1 (0.1%)
High-Ceiling Diuretics And Potassium-Sparing Agents	Any	1 (0.1%)
	SALMETEROL XINAFOATE	1 (0.1%)
Hmg Coa Reductase Inhibitors	Any	271 (17.4%)
	AMLODIPINE BESILATE~ATORVASTATIN CALCIUM	1 (0.1%)
	ATORVASTATIN CALCIUM	108 (6.9%)
	FENOFIBRATE	2 (0.1%)
	FENOFIBRATE~PRAVASTATIN SODIUM	5 (0.3%)
	FLUVASTATIN SODIUM	2 (0.1%)
	PITAVASTATIN CALCIUM	2 (0.1%)
	PRAVASTATIN SODIUM	12 (0.8%)
	ROSUVASTATIN CALCIUM	26 (1.7%)
	SIMVASTATIN	114 (7.3%)
Hmg Coa Reductase Inhibitors In Combination With Other Lipid Modifying Agents	Any	6 (0.4%)
	EZETIMIBE~SIMVASTATIN	6 (0.4%)
Hmg Coa Reductase Inhibitors, Other Combinations	Any	6 (0.4%)
	ACETYLSALICYLIC ACID - ATORVASTATIN CALCIUM - RAMIPRIL	2 (0.1%)
	AMLODIPINE BESILATE~PERINDOPRIL ARGININE	4 (0.3%)
Hmg-Coa Reduttasi.	Any	2 (0.1%)
	FENOFIBRATE	2 (0.1%)
Homeophaty	Any	21 (1.3%)
	AMLODIPINE BESILATE~OLMESARTAN MEDOXOMIL	3 (0.2%)
	ANAMIRTA COCCULUS ~CONIUM MACULATUM~ HOMEOPATHICS NOS	1 (0.1%)
	ASCORBIC ACID~COPPER~CYANOCOBALAMIN~FOLIC ACID~MANGANESE~NICOTINAMIDE~OMEGA-3 FATTY ACIDS~PYRIDOXINE HYDROCHLORIDE~RETINOL~RIBOFLAVIN~SELENIUM~THIAMINE HYDROCHLORIDE~TOCOPHEROL~XANTOFYL~ZEAXANTHIN~ZINC	1 (0.1%)
	CAMPHOR	1 (0.1%)
	CANNABIS SATIVA	3 (0.2%)
	EUPHRASIA OFFICINALIS	1 (0.1%)
	GINKGO BILOBA EXTRACT	1 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	GINKOBILOBA EXTRACT	1 (0.1%)
	MAGNESIUM HYDROGEN ASPARTATE~POTASSIUM ASPARTATE	1 (0.1%)
	PLANTAGO OVATA	2 (0.1%)
	PLANTAGO PSYLLIUM	1 (0.1%)
	SERENOA REPENS EXTRACT	3 (0.2%)
	VALERIANA OFFICINALIS EXTRACT	2 (0.1%)
Hormones	Any	2 (0.1%)
	TESTOSTERONE	1 (0.1%)
	TESTOSTERONE UNDECANOATE	1 (0.1%)
Human Immunoglobulines	Any	1 (0.1%)
	IMMUNOGLOBULIN HUMAN NORMAL	1 (0.1%)
Hypocalor Antireflux Syrup	Any	1 (0.1%)
	ALTHAEA OFFICINALIS~DEXPANTHENOL~MAGNESIUM ALGINATE~PAPAVER RHOEAS~SIMETICONE~SODIUM CARBONATE MONOHYDRATE~ZINC OXIDE	1 (0.1%)
Imidazole And Triazole Derivatives	Any	1 (0.1%)
	ACETYLCYSTEINE	1 (0.1%)
Imidazole Derivatives	Any	1 (0.1%)
	METRONIDAZOLE	1 (0.1%)
Imidazoline Receptor Agonists	Any	6 (0.4%)
	CLONIDINE HYDROCHLORIDE	1 (0.1%)
	MOXONIDINE	5 (0.3%)
Immunoglobulins, Normal Human	Any	1 (0.1%)
	IMMUNOGLOBULIN G HUMAN	1 (0.1%)
Immunostimulant	Any	1 (0.1%)
	ANTIBIOTIC	1 (0.1%)
Insulins And Analogues For Injection	Any	17 (1.1%)
	INSULIN	5 (0.3%)
	INSULIN ASPART	1 (0.1%)
	INSULIN BOVINE	6 (0.4%)
	INSULIN HUMAN	3 (0.2%)
	INSULIN HUMAN INJECTION, ISOPHANE	1 (0.1%)
	INSULIN LISPRO	1 (0.1%)
Insulins And Analogues For Injection, Fast-Acting	Any	9 (0.6%)
	INSULIN GLULISINE	3 (0.2%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	INSULIN HUMAN	2 (0.1%)
	INSULIN LISPRO	3 (0.2%)
	INSULIN LISPRO~INSULIN LISPRO PROTAMINE SUSPENSION	1 (0.1%)
Insulins And Analogues For Injection, Intermediate- Or Long-Acting Combined With Fast-Acting	Any	1 (0.1%)
	INSULIN HUMAN~INSULIN HUMAN INJECTION, ISOPHANE	1 (0.1%)
Insulins And Analogues For Injection, Intermediate-Acting	Any	1 (0.1%)
	INSULIN HUMAN INJECTION, ISOPHANE	1 (0.1%)
Insulins And Analogues For Injection, Long-Acting	Any	15 (1.0%)
	INSULIN DEGLUDEC	2 (0.1%)
	INSULIN GLARGINE	13 (0.8%)
Iron	Any	2 (0.1%)
	FERRIC HYDROXIDE POLYMALTOSE COMPLEX~FOLIC ACID	1 (0.1%)
	FERROUS SULFATE	1 (0.1%)
Iron Bivalent, Oral Preparations	Any	6 (0.4%)
	FERROGRAD	3 (0.2%)
	FERROUS SULFATE	3 (0.2%)
Iron In Other Combinations	Any	2 (0.1%)
	FERFOLIC	1 (0.1%)
	NIFEREX	1 (0.1%)
Iron Preparations	Any	1 (0.1%)
	IRON	1 (0.1%)
Iron Trivalent, Oral Preparations	Any	2 (0.1%)
	FERRIMANNITOL OVALBUMIN	1 (0.1%)
	IRON SUCCINYL-PROTEIN COMPLEX	1 (0.1%)
Laxative	Any	50 (3.2%)
	MACROGOL 3350~POTASSIUM CHLORIDE~SODIUM BICARBONATE~SODIUM CHLORIDE	48 (3.1%)
	SENNOSIDE A+B	3 (0.2%)
Leukotriene Receptor Antagonists	Any	1 (0.1%)
	MONTELUKAST SODIUM	1 (0.1%)
Lincosamides	Any	1 (0.1%)
	CLINDAMYCIN	1 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
Local Anesthetic	Any	1 (0.1%)
	EPINEPHRINE~LIDOCAINE HYDROCHLORIDE	1 (0.1%)
Low-Ceiling Diuretics And Potassium-Sparing Agents	Any	2 (0.1%)
	AMILORIDE HYDROCHLORIDE~HYDROCHLOROTHIAZIDE	1 (0.1%)
	BUTIZIDE~POTASSIUM CANRENOATE	1 (0.1%)
Macrolides	Any	3 (0.2%)
	CLARITHROMYCIN	1 (0.1%)
	ERYTHROMYCIN	1 (0.1%)
	GLICLAZIDE	1 (0.1%)
Magnesium	Any	16 (1.0%)
	ALUMINIUM HYDROXIDE~MAGNESIUM HYDROXIDE	4 (0.3%)
	MAGNEPAMYL	1 (0.1%)
	MAGNESIUM	1 (0.1%)
	MAGNESIUM ASPARTATE	1 (0.1%)
	MAGNESIUM ASPARTATE HYDROCHLORIDE	3 (0.2%)
	MAGNESIUM CITRATE	4 (0.3%)
	MAGNESIUM~MAGNESIUM CARBONATE~MAGNESIUM CITRATE~MAGNESIUM PHOSPHATE	2 (0.1%)
Magnesium Compounds	Any	1 (0.1%)
	MAGNESIUM HYDROXIDE	1 (0.1%)
Medical Plants	Any	1 (0.1%)
	ASCORBIC ACID~CURCUMIN	1 (0.1%)
Melatonin	Any	34 (2.2%)
	MELATONIN	34 (2.2%)
Melatonin Receptor Agonists	Any	1 (0.1%)
	MELATONIN	1 (0.1%)
Methanolquinolines	Any	1 (0.1%)
	QUININE SULFATE	1 (0.1%)
Mineralcorticoids	Any	6 (0.4%)
	FLUDROCORTISONE	5 (0.3%)
	FLUDROCORTISONE ACETATE	1 (0.1%)
Monoclonal Antibodies	Any	1 (0.1%)
	BEVACIZUMAB	1 (0.1%)
Monoclonal Antibody	Any	1 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	RITUXIMAB	1 (0.1%)
Mucolytics	Any	6 (0.4%)
	ACETYLCYSTEINE	3 (0.2%)
	AMBROXOL	1 (0.1%)
	CARBOCISTEINE	2 (0.1%)
Multivitamins With Minerals	Any	1 (0.1%)
	ASCORBIC ACID~BIOTIN~CALCIUM PANTOTHENATE~CALCIUM PHOSPHATE~COPPER SULFATE~CYANOCOBALAMIN~DL-ALPHA TOCOPHERYL ACETATE~ERGOCALCIFEROL~IRON~MAGNESIUM OXIDE~MAGNESIUM PHOSPHATE~MAGNESIUM STEARATE~MANGANESE SULFATE~MOLYBDENUM~NICOTINAMIDE~PHOSPHORUS~PYRIDOXINE HYDROCHLORIDE~RETINOL~RIBOFLAVIN~THIAMINE H	1 (0.1%)
Muscle Relaxants	Any	2 (0.1%)
	AMITRIPTYLINE HYDROCHLORIDE~PERPHENAZINE	1 (0.1%)
	GLYCERYL TRINITRATE	1 (0.1%)
Natural And Semisynthetic Estrogens, Plain	Any	1 (0.1%)
	ESTRADIOL~LEVONORGESTREL	1 (0.1%)
Natural Opium Alkaloids	Any	16 (1.0%)
	NALOXONE HYDROCHLORIDE~OXYCODONE HYDROCHLORIDE	11 (0.7%)
	OXYCODONE	2 (0.1%)
	OXYCODONE HYDROCHLORIDE	3 (0.2%)
Nitrofuran Derivatives	Any	1 (0.1%)
	NITROFURANTOIN	1 (0.1%)
Nitrogen Mustard Analogues	Any	1 (0.1%)
	CHLORAMBUCIL	1 (0.1%)
Non-Selective Monoamine Reuptake Inhibitors	Any	3 (0.2%)
	AMITRIPTYLINE HYDROCHLORIDE~MEDAZEPAM	2 (0.1%)
	NORTRIPTYLINE HYDROCHLORIDE	1 (0.1%)
Non-Steroids Antinflammatory Drugs	Any	3 (0.2%)
	DICLOFENAC EPOLAMINE	1 (0.1%)
	DICLOFENAC SODIUM	1 (0.1%)
	DICLOFENAC SODIUM~MISOPROSTOL	1 (0.1%)
Nonsteroidal Anti-Inflammatory Drug	Any	26 (1.7%)
	ACETYLSALICYLIC ACID	17 (1.1%)
	IBUPROFEN	9 (0.6%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
Not Classifiable	Any	4 (0.3%)
	GASTRIC BALLOON FOR OBESITY	1 (0.1%)
	RONANE	1 (0.1%)
	UNKNOWN SECRETOLYTIC TREATMENT	1 (0.1%)
	UNKNOWN SPRAY FOR INHALATION FOR TREATMENT OF COPD	1 (0.1%)
Nucleosides And Nucleotides Excl. Reverse Transcriptase Inhibitors	Any	1 (0.1%)
	VALACICLOVIR HYDROCHLORIDE	1 (0.1%)
Opioid Anesthetics	Any	1 (0.1%)
	SUFENTANIL	1 (0.1%)
Opioids In Combination With Non-Opioid Analgesics	Any	5 (0.3%)
	PARACETAMOL~TRAMADOL	1 (0.1%)
	PARACETAMOL~TRAMADOL HYDROCHLORIDE	4 (0.3%)
Organic Nitrates	Any	17 (1.1%)
	GLYCERYL TRINITRATE	10 (0.6%)
	ISOSORBIDE DINITRATE	1 (0.1%)
	ISOSORBIDE MONONITRATE	6 (0.4%)
Oripavine Derivatives	Any	4 (0.3%)
	BUPRENORPHINE	4 (0.3%)
Osmotically Acting Laxatives	Any	38 (2.4%)
	ELECTROLYTES NOS~MACROGOL 4000	1 (0.1%)
	GALACTOSE~LACTOSE~LACTULOSE	3 (0.2%)
	LACTULOSE	9 (0.6%)
	MACROGOL	15 (1.0%)
	MACROGOL 3350~POTASSIUM CHLORIDE~SODIUM BICARBONATE~SODIUM CHLORIDE	4 (0.3%)
	MACROGOL 400	1 (0.1%)
	MACROGOL 4000	5 (0.3%)
Other Anti-Dementia Drugs	Any	10 (0.6%)
	MEMANTINE	1 (0.1%)
	MEMANTINE HYDROCHLORIDE	9 (0.6%)
Other Antianemic Preparations	Any	4 (0.3%)
	DARBEPOETIN ALFA	3 (0.2%)
	EPOETIN ALFA	1 (0.1%)
Other Antibacterials	Any	2 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	FOSFOMYCIN	1 (0.1%)
	FOSFOMYCIN TROMETAMOL	1 (0.1%)
Other Antiemetics	Any	2 (0.1%)
	DRONABINOL	2 (0.1%)
Other Antiepileptics	Any	119 (7.6%)
	CARBAMAZEPINE	1 (0.1%)
	ESLICARBAZEPINE ACETATE	1 (0.1%)
	GABAPENTIN	30 (1.9%)
	LAMOTRIGINE	2 (0.1%)
	LEVETIRACETAM	6 (0.4%)
	OXCARBAZEPINE	3 (0.2%)
	PHENOBARBITAL SODIUM	2 (0.1%)
	PREGABALIN	73 (4.7%)
	PRIMIDONE	1 (0.1%)
	TOPIRAMATE	3 (0.2%)
	ZONISAMIDE	1 (0.1%)
Other Antifungals For Topical Use	Any	2 (0.1%)
	CICLOPIROX OLAMINE	1 (0.1%)
	TERBINAFINE HYDROCHLORIDE	1 (0.1%)
Other Antihistamines For Systemic Use	Any	6 (0.4%)
	BILASTINE	1 (0.1%)
	DESLORATADINE	2 (0.1%)
	EBASTINE	2 (0.1%)
	TAMSULOSIN HYDROCHLORIDE	1 (0.1%)
Other Antiinflammatory And Antirheumatic Agents, Non-Steroids	Any	10 (0.6%)
	AMINOPHENAZONE - CAMYLOFIN - CHLORPHENOXAMINE - EPHEDRINE - ETAMIPHYLLIN	1 (0.1%)
	CHONDROITIN SULFATE	4 (0.3%)
	CHONDROITIN SULFATE SODIUM	3 (0.2%)
	GLUCOSAMINE SULFATE	2 (0.1%)
Other Antineoplastic Agents	Any	9 (0.6%)
	CELECOXIB	6 (0.4%)
	HYDROXYCARBAMIDE	3 (0.2%)
Other Antipsoriatics For Topical Use	Any	1 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	BETAMETHASONE DIPROPIONATE~CALCIPOTRIOL	1 (0.1%)
Other Antipsychotics	Any	2 (0.1%)
	ARIPIPRAZOLE	2 (0.1%)
Other Antithrombotic Agents	Any	4 (0.3%)
	WARFARIN SODIUM	4 (0.3%)
Other Blood Glucose Lowering Drugs, Excl. Insulins	Any	2 (0.1%)
	REPAGLINIDE	2 (0.1%)
Other Blood Glucose Lowering Drugs, Excluding Insulins	Any	1 (0.1%)
	REPAGLINIDE	1 (0.1%)
Other Capillary Stabilizing Agents	Any	1 (0.1%)
	NAFTAZONE	1 (0.1%)
Other Cardiac Preparations	Any	10 (0.6%)
	IVABRADINE	1 (0.1%)
	IVABRADINE HYDROCHLORIDE	6 (0.4%)
	RANOLAZINE	4 (0.3%)
	UBIDECARENONE	1 (0.1%)
Other Centrally Acting Agents	Any	5 (0.3%)
	BACLOFEN	3 (0.2%)
	CHLORMEZANONE~THIOCOLCHICOSIDE	1 (0.1%)
	CYCLOBENZAPRINE HYDROCHLORIDE	1 (0.1%)
Other Dermatologicals	Any	8 (0.5%)
	FINASTERIDE	8 (0.5%)
Other Drugs Affecting Bone Structure And Mineralization	Any	7 (0.4%)
	DENOSUMAB	7 (0.4%)
Other Drugs For Constipation	Any	2 (0.1%)
	LINACLOTIDE	1 (0.1%)
	PRUCALOPRIDE SUCCINATE	1 (0.1%)
Other Drugs For Functional Gastrointestinal Disorders	Any	4 (0.3%)
	DICYCLOVERINE HYDROCHLORIDE~PARACETAMOL	4 (0.3%)
Other Estrogens	Any	1 (0.1%)
	TIBOLONE	1 (0.1%)
Other Herbal	Any	22 (1.4%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	ANGELICA ARCHANGELICA ROOT~CARUM CARVI FRUIT~CHELIDONIUM MAJUS HERB~GLYCYRRHIZA GLABRA ROOT~IBERIS AMARA~MATRICARIA RECUTITA FLOWER~MELISSA OFFICINALIS LEAF~MENTHA X PIPERITA LEAF~SILYBUM MARIANUM FRUIT	1 (0.1%)
	CRANBERRY EXTRACT AND ACEROLA VITAMIN C	1 (0.1%)
	CRATAEGUS LAEVIGATA EXTRACT	1 (0.1%)
	D-MANNOSE~VACCINIUM MACROCARPON	1 (0.1%)
	DOXYLAMINE SUCCINATE	1 (0.1%)
	DRY EXTRACT FROM VALERIAN ROOT	4 (0.3%)
	EXTRACT FROM STRYCHNOS NUX-VOMICA SEEDS (OMEOPATIA)	2 (0.1%)
	GINKGO BILOBA	2 (0.1%)
	GINKGO BILOBA EXTRACT	2 (0.1%)
	PHYTOPHARMACEUTICAL	1 (0.1%)
	PLANTAGO OVATA	1 (0.1%)
	REMIFENTANIL HYDROCHLORIDE	1 (0.1%)
	SALVIA OFFICINALIS	1 (0.1%)
	SALVIA OFFICINALIS LEAF	1 (0.1%)
	SERENOA REPENS	3 (0.2%)
	SERENOA REPENS EXTRACT	1 (0.1%)
Other Hypnotics And Sedatives	Any	5 (0.3%)
	AVENA SATIVA~ESCHSCHOLZIA CALIFORNICA EXTRACT~HUMULUS LUPULUS EXTRACT~MAGNESIUM PHOSPHATE DIBASIC~PASSIFLORA INCARNATA EXTRACT~POTASSIUM PHOSPHATE DIBASIC~SODIUM PHOSPHATE DIBASIC~VALERIANA OFFICINALIS EXTRACT	1 (0.1%)
	CLOMETHIAZOLE	4 (0.3%)
Other Immunosuppressants	Any	5 (0.3%)
	AZATHIOPRINE	3 (0.2%)
	METHOTREXATE SODIUM	1 (0.1%)
	REUMAFLEX	1 (0.1%)
Other Lipid Modifying Agents	Any	18 (1.2%)
	EZETIMIBE	12 (0.8%)
	EZETIMIBE~SIMVASTATIN	1 (0.1%)
	OMEGA-3 TRIGLYCERIDES	3 (0.2%)
	OMEGA-3-ACID ETHYL ESTER	1 (0.1%)
	RICE POLYCOSANOLS~FERMENDED RED RICE~PLANT STEROLS~ EXTRAMEL ~ PROANTHOCYANIDINS FORM RED GRAPE EXTRACT~OLIVEX~FOLIC ACID	1 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
Other Nasal Preparations	Any	2 (0.1%)
	IPRATROPIUM BROMIDE	1 (0.1%)
	MUPIROCIN	1 (0.1%)
Other Ophthalmologicals	Any	1 (0.1%)
	ASCORBIC ACID - CUPRIC OXIDE - TOCOPHERYL ACETATE - XANTOFYL - ZINC OXIDE	1 (0.1%)
Other Opioids	Any	46 (3.0%)
	DEXKETOPROFEN TROMETAMOL~TRAMADOL HYDROCHLORIDE	1 (0.1%)
	NALOXONE~TILIDINE	1 (0.1%)
	PARACETAMOL~TRAMADOL HYDROCHLORIDE	9 (0.6%)
	TAPENTADOL	5 (0.3%)
	TAPENTADOL HYDROCHLORIDE	5 (0.3%)
	TRAMADOL	18 (1.2%)
	TRAMADOL HYDROCHLORIDE	10 (0.6%)
Other Plain Vitamin Preparations	Any	3 (0.2%)
	BIOTIN	1 (0.1%)
	OMEGA-3~OMEGA-6 SERIES~VITAMINS E~C~B6~B12~ZINC	1 (0.1%)
	PYRIDOXINE HYDROCHLORIDE	1 (0.1%)
Other Psychostimulants And Nootropics	Any	5 (0.3%)
	CITICOLINE	1 (0.1%)
	CYANOCOBALAMIN~FISH OIL~FOLIC ACID~PYRIDOXINE HYDROCHLORIDE	3 (0.2%)
	PIRACETAM	1 (0.1%)
Other Sclerosing Agents	Any	2 (0.1%)
	CALCIUM DOBESILATE	2 (0.1%)
Other Systemic Drugs For Obstructive Airway Diseases	Any	1 (0.1%)
	ROFLUMILAST	1 (0.1%)
Other Systemic Hemostatics	Any	1 (0.1%)
	ELTROMBOPAG OLAMINE	1 (0.1%)
Other Treatments No Pd	Any	1 (0.1%)
	CLARITHROMYCIN	1 (0.1%)
Other Vasodilators Used In Cardiac Diseases	Any	2 (0.1%)
	HEPTAMINOL HYDROCHLORIDE	1 (0.1%)
	MOLSIDOMINE	1 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
Others	Any	11 (0.7%)
	BOTULINUM TOXIN TYPE A	11 (0.7%)
Oxicams	Any	4 (0.3%)
	MELOXICAM	4 (0.3%)
Pancreatic Enzyme Product	Any	1 (0.1%)
	PANCREATIN	1 (0.1%)
Parathyroid Hormones And Analogues	Any	2 (0.1%)
	TERIPARATIDE	2 (0.1%)
Penicillins With Extended Spectrum	Any	3 (0.2%)
	AMOXICILLIN TRIHYDRATE	1 (0.1%)
	AMOXICILLIN TRIHYDRATE~CLAVULANATE POTASSIUM	1 (0.1%)
	PIPERACILLIN	1 (0.1%)
Peripherally Acting Antiobesity Products	Any	1 (0.1%)
	ORLISTAT	1 (0.1%)
Phenothiazines With Aliphatic Side-Chain	Any	1 (0.1%)
	PROMAZINE HYDROCHLORIDE	1 (0.1%)
Phenylalkylamine Derivatives	Any	3 (0.2%)
	VERAPAMIL HYDROCHLORIDE	3 (0.2%)
Phenylpiperidine Derivatives	Any	12 (0.8%)
	FENTANYL	12 (0.8%)
Piperazine Derivatives	Any	9 (0.6%)
	CAFFEINE~MECLOZINE HYDROCHLORIDE MONOHYDRATE~PYRIDOXINE HYDROCHLORIDE	2 (0.1%)
	CETIRIZINE HYDROCHLORIDE	4 (0.3%)
	CYCLIZINE LACTATE	2 (0.1%)
	LEVOCETIRIZINE DIHYDROCHLORIDE	2 (0.1%)
Platelet Aggregation Inhibitors Excluding Heparin	Any	114 (7.3%)
	ACETYLSALICYLIC ACID	60 (3.9%)
	ACETYLSALICYLIC ACID~CLOPIDOGREL BISULFATE	4 (0.3%)
	ACETYLSALICYLIC ACID~DIPYRIDAMOLE	1 (0.1%)
	CILOSTAZOL	1 (0.1%)
	CLOPIDOGREL BISULFATE	12 (0.8%)
	CLOPIDOGREL HYDROCHLORIDE	25 (1.6%)
	DIPYRIDAMOLE	1 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	INDOBUFEN	1 (0.1%)
	TICAGRELOR	2 (0.1%)
	TICLOPIDINE HYDROCHLORIDE	4 (0.3%)
	TRIFLUSAL	6 (0.4%)
Platinum Compounds	Any	2 (0.1%)
	CARBOPLATIN	2 (0.1%)
Potassium	Any	6 (0.4%)
	ASCORBIC ACID~POTASSIUM BICARBONATE	1 (0.1%)
	POTASSIUM	1 (0.1%)
	POTASSIUM CHLORIDE	2 (0.1%)
	POTASSIUM CITRATE	2 (0.1%)
Preparations Inhibiting Uric Acid Production	Any	36 (2.3%)
	ALLOPURINOL	36 (2.3%)
Propionic Acid Derivatives	Any	40 (2.6%)
	DEXIBUPROFEN	1 (0.1%)
	DEXKETOPROFEN	1 (0.1%)
	DEXKETOPROFEN TROMETAMOL	7 (0.4%)
	ESOMEPRAZOLE MAGNESIUM~NAPROXEN	2 (0.1%)
	IBUPROFEN	29 (1.9%)
	KETOPROFEN LYSINE	1 (0.1%)
Propulsives	Any	81 (5.2%)
	DOMPERIDONE	78 (5.0%)
	LEVOSULPIRIDE	1 (0.1%)
	METOCLOPRAMIDE	2 (0.1%)
Prostaglandin Analogues	Any	22 (1.4%)
	ALPROSTADIL	1 (0.1%)
	BIMATOPROST	4 (0.3%)
	LATANOPROST	11 (0.7%)
	TAFLUPROST	1 (0.1%)
	TRAVOPROST	5 (0.3%)
Protein Kinase Inhibitors	Any	2 (0.1%)
	IBRUTINIB	2 (0.1%)
Proton Pump Inhibitors	Any	379 (24.3%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	DEXPANTHENOL	15 (1.0%)
	ERYTHROMYCIN ETHYLSUCCINATE - SULFAFURAZOLE	14 (0.9%)
	ESOMEPRAZOLE	9 (0.6%)
	ESOMEPRAZOLE MAGNESIUM	24 (1.5%)
	HYDROCHLOROTHIAZIDE~OLMESARTAN MEDOXOMIL	1 (0.1%)
	LANSOPRAZOLE	49 (3.1%)
	OMEPRAZOLE	168 (10.8%)
	OMEPRAZOLE MAGNESIUM	1 (0.1%)
	PANTOPRAZOLE	67 (4.3%)
	PANTOPRAZOLE SODIUM SESQUIHYDRATE	33 (2.1%)
	PROTON PUMP INHIBITOR	1 (0.1%)
	RABEPRAZOLE	1 (0.1%)
	RABEPRAZOLE SODIUM	4 (0.3%)
Purine Derivatives	Any	1 (0.1%)
	PENTOXIFYLLINE	1 (0.1%)
Pyrazolones	Any	52 (3.3%)
	METAMIZOLE MAGNESIUM	29 (1.9%)
	METAMIZOLE SODIUM	25 (1.6%)
Pyrimidine Analogues	Any	1 (0.1%)
	FLUOROURACIL	1 (0.1%)
Quinine And Derivatives	Any	2 (0.1%)
	AMINOPHYLLINE~QUININE SULFATE	1 (0.1%)
	QUININE	1 (0.1%)
Renin-Inhibitors	Any	1 (0.1%)
	ALISKIREN FUMARATE	1 (0.1%)
Salicylic Acid And Derivatives	Any	206 (13.2%)
	ACETYLSALICYLATE LYSINE	8 (0.5%)
	ACETYLSALICYLIC ACID	193 (12.4%)
	ACETYLSALICYLIC ACID~ALUMINIUM HYDROXIDE~MAGNESIUM HYDROXIDE	5 (0.3%)
Saponin	Any	1 (0.1%)
	FLEBOSTATIN	1 (0.1%)
Second-Generation Cephalosporins	Any	3 (0.2%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	CEFUROXIME	3 (0.2%)
Selective Beta-2-Adrenoreceptor Agonists	Any	10 (0.6%)
	FORMOTEROL	2 (0.1%)
	GLYCOPYRRONIUM BROMIDE~INDACATEROL MALEATE	2 (0.1%)
	GUAIFENESIN~SALBUTAMOL SULFATE	1 (0.1%)
	SALBUTAMOL	5 (0.3%)
Selective Estrogen Receptor Modulators	Any	3 (0.2%)
	RALOXIFENE	2 (0.1%)
	RALOXIFENE HYDROCHLORIDE	1 (0.1%)
Selective Immunosuppressants	Any	2 (0.1%)
	LEFLUNOMIDE	1 (0.1%)
	MYCOPHENOLATE MOFETIL	1 (0.1%)
Selective Serotonin (5ht1) Agonists	Any	3 (0.2%)
	RIZATRIPTAN BENZOATE	2 (0.1%)
	SUMATRIPTAN SUCCINATE	1 (0.1%)
Serotonin (5ht3) Antagonists	Any	1 (0.1%)
	ONDANSETRON	1 (0.1%)
Snri	Any	108 (6.9%)
	DESVENLAFAXINE	4 (0.3%)
	DESVENLAFAXINE SUCCINATE	5 (0.3%)
	DULOXETINE	20 (1.3%)
	DULOXETINE HYDROCHLORIDE	40 (2.6%)
	VENLAFAXINE HYDROCHLORIDE	42 (2.7%)
Sodium-Glucose Co-Transporter 2 (Sglt2) Inhibitors	Any	1 (0.1%)
	EMPAGLIFLOZIN	1 (0.1%)
Softeners, Emollients	Any	2 (0.1%)
	CHONDRUS CRISPUS~PARAFFIN	1 (0.1%)
	PARAFFIN, LIQUID~PHENOLPHTHALEIN	1 (0.1%)
Ssri	Any	233 (15.0%)
	CITALOPRAM HYDROBROMIDE	39 (2.5%)
	ESCITALOPRAM OXALATE	82 (5.3%)
	FLUCONAZOLE	1 (0.1%)
	FLUOXETINE HYDROCHLORIDE	3 (0.2%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	PAROXETINE	9 (0.6%)
	PAROXETINE HYDROCHLORIDE	33 (2.1%)
	SERTRALINE	23 (1.5%)
	SERTRALINE HYDROCHLORIDE	48 (3.1%)
Statins	Any	4 (0.3%)
	LOVASTATIN	1 (0.1%)
	PITAVASTATIN	1 (0.1%)
	ROSUVASTATIN	1 (0.1%)
	ROSUVASTATIN CALCIUM	1 (0.1%)
Sulfonamides, Plain	Any	95 (6.1%)
	ATENOLOL INDIPAMIDE	1 (0.1%)
	BUMETANIDE	3 (0.2%)
	CHLORTALIDONE	6 (0.4%)
	ENOXPARIN SODIUM	1 (0.1%)
	FUROSEMIDE	53 (3.4%)
	INDAPAMIDE	6 (0.4%)
	PIRETANIDE	1 (0.1%)
	TORASEMIDE	25 (1.6%)
	XIPAMIDE	1 (0.1%)
Sulfonylureas	Any	29 (1.9%)
	GLIBENCLAMIDE	3 (0.2%)
	GLICLAZIDE	17 (1.1%)
	GLIMEPIRIDE	8 (0.5%)
	GLIQUIDONE	2 (0.1%)
Sulphur-Containing Imidazole Derivatives	Any	5 (0.3%)
	THIAMAZOLE	5 (0.3%)
Taxanes	Any	1 (0.1%)
	PACLITAXEL	1 (0.1%)
Testosterone-5-Alpha Reductase Inhibitors	Any	37 (2.4%)
	DUTASTERIDE	32 (2.1%)
	FINASTERIDE	5 (0.3%)
Tests For Fertility Disturbances	Any	2 (0.1%)
	GONADORELIN	2 (0.1%)
Thiazides	Any	2 (0.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	BENDROFLUMETHIAZIDE	2 (0.1%)
Thiazides, Plain	Any	26 (1.7%)
	ENALAPRIL MALEATE~HYDROCHLOROTHIAZIDE	2 (0.1%)
	HYDROCHLOROTHIAZIDE	24 (1.5%)
Third Generation Cephalosporins	Any	3 (0.2%)
	CEFDITOREN	1 (0.1%)
	CEFTAZIDIME	1 (0.1%)
	CEFTRIAXONE	2 (0.1%)
Thyroid Hormones	Any	126 (8.1%)
	LEVOTHYROXINE	10 (0.6%)
	LEVOTHYROXINE SODIUM	114 (7.3%)
	LEVOTHYROXINE SODIUM~POTASSIUM IODIDE	2 (0.1%)
Triazole Derivatives	Any	1 (0.1%)
	FLUCONAZOLE	1 (0.1%)
Tumor Necrosis Factor Alpha (Tnf-) Inhibitors	Any	1 (0.1%)
	ADALIMUMAB	1 (0.1%)
Tumor Necrosis Factor Alpha (Tnf-Alfa) Inhibitors	Any	1 (0.1%)
	GOLIMUMAB	1 (0.1%)
Vasopressin And Analogues	Any	1 (0.1%)
	DESMOPRESSIN ACETATE	1 (0.1%)
Viscoelastic Substances	Any	2 (0.1%)
	HYALURONATE SODIUM	1 (0.1%)
	HYPROMELLOSE	1 (0.1%)
Vitamin B-Complex, Plain	Any	2 (0.1%)
	VITAMIN B KOMPLEX	1 (0.1%)
	VITAMIN B-COMPLEX	1 (0.1%)
Vitamin B1 In Combination With Vitamin B6 And/Or Vitamin B12	Any	2 (0.1%)
	BENEXOL B12	1 (0.1%)
	CYANOCOBALAMIN~PYRIDOXINE HYDROCHLORIDE~RIBOFLAVIN~THIAMINE MONONITRATE	1 (0.1%)
Vitamin B12 (Cyanocobalamin And Analogues)	Any	28 (1.8%)
	COBAMAMIDE	17 (1.1%)

	ACTIVE	Total number of evaluable patients (FAS) (N= 1558)
	CYANOCOBALAMIN	7 (0.4%)
	CYANOCOBALAMIN~FOLIC ACID	1 (0.1%)
	CYANOCOBALAMIN~FOLIC ACID~PYRIDOXINE HYDROCHLORIDE	1 (0.1%)
	CYANOCOBALAMIN~LECITHIN~LIDOCAINE HYDROCHLORIDE	1 (0.1%)
	PYRIDOXINE HYDROCHLORIDE	1 (0.1%)
Vitamin D And Analogues	Any	121 (7.8%)
	ACETYLSALICYLIC ACID~SIMVASTATIN	3 (0.2%)
	ACTIVE METABOLITE OF VITAMIN D	1 (0.1%)
	CALCIFEDIOL	26 (1.7%)
	CALCITRIOL	3 (0.2%)
	CALCIUM CARBONATE~COLECALCIFEROL	5 (0.3%)
	CALCIUM CARBONATE~ERGOCALCIFEROL	2 (0.1%)
	COLECALCIFEROL	80 (5.1%)
	COLECALCIFEROLO	1 (0.1%)
	ERGOCALCIFEROL	1 (0.1%)
Vitamin K Antagonists	Any	34 (2.2%)
	ACENOCOUMAROL	23 (1.5%)
	PHENPROCOUMON	6 (0.4%)
	WARFARIN	1 (0.1%)
	WARFARIN SODIUM	4 (0.3%)
Vitamins	Any	3 (0.2%)
	CYANOCOBALAMIN	2 (0.1%)
	RETINOL	1 (0.1%)
Vitamins, Other Combinations	Any	3 (0.2%)
	AMMONIUM CHLORIDE~DIPHENHYDRAMINE HYDROCHLORIDE	1 (0.1%)
	CALCIUM LEVOMEFOLATE~CYANOCOBALAMIN~MAGNESIUM~MAGNESIUM GLYCEROPHOSPHATE~PYRIDOXINE HYDROCHLORIDE~TAURINE	2 (0.1%)
Xanthines	Any	3 (0.2%)
	BAMIFYLLINE HYDROCHLORIDE	1 (0.1%)
	PENTOXIFYLLINE	2 (0.1%)
Xanthines Derivatives	Any	3 (0.2%)
	CAFFEINE CITRATE~GLYCERYL TRINITRATE	3 (0.2%)

Note. Percentages were computed out of the total number of patients evaluable for the FAS. A patient could receive more than one treatment for any other concomitant condition.

Table A3. SAEs listing during observation

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
74	Male	Yes	No	2016-10-26	2017-12-01	Disease progression	One tablet -50 mg	Cardiac disorders	Coronary artery occlusion	2017-06-01	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-07-NK	Unlikely	None
74	Female	No	No	2016-12-15	2017-07-17	Other - Shoulder surgery	One tablet -50 mg	Injury, poisoning and procedural complications	Joint dislocation	2017-07-04	Severe	New/ Prolonged hospitalization	Recovered/ resolved with sequelae	2017-10-31	Possible	Drug permanentl y interrupted
79	Male	Yes	No	2017-05-25	Ongoing		One tablet -50 mg	Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Non-Hodgkin's lymphoma	2018-08-03	Severe	Other important medical event	Not recovered/ not resolved		Not Related	None
55	Male	Yes	No	2017-06-22	Ongoing		One tablet -50 mg	Infections and infestations	Varicella zoster virus infection	2017-07-03	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-07-26	Unlikely	None
69	Female	Yes	No	2018-01-16	Ongoing		One tablet -50 mg	General disorders and administration site conditions	Therapeutic response shortened	2018-09-25	Mild	New/ Prolonged hospitalization	Recovering /resolving		Unlikely	None
60	Female	No	Yes	2016-10-03	2016-11-28	Adverse reaction	One tablet -50 mg	Nervous system disorders	Dyskinesia	2016-11-28	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2016-12-06	Probable	Drug permanentl y interrupted
74	Female	Yes	Yes	2016-10-12	2017-02-02	Disease progression	One tablet -50 mg	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	2016-11-22	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2016-11-30	Not Related	None
80	Female	Yes	No	2017-02-22	Ongoing		One tablet -50 mg	Gastrointestinal disorders	Faecaloma	2017-12-01	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2018-03-01	Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
69	Female	Yes	Yes	2017-05-24	Ongoing		One tablet -50 mg	Infections and infestations	Urinary tract infection	2017-11-07	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2017-11-08	Not Related	None
75	Male	Yes	Yes	2017-06-14	Ongoing		One tablet -50 mg	Infections and infestations	Pneumonia	2018-01-27	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2018-02-07	Not Related	None
74	Female	Yes	No	2017-09-15	Ongoing		One tablet -50 mg	Nervous system disorders	Sciatica	2017-11-07	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-11-13	Not Related	None
81	Male	Yes	No	2016-10-14	Ongoing		One tablet -50 mg	Nervous system disorders	Cognitive disorder	2017-05-29	Moderate	New/ Prolonged hospitalization	Not recovered/ not resolved		Not Related	None
85	Male	Yes	No	2016-11-17	Ongoing		One tablet -50 mg	Infections and infestations	Pneumonia	2017-06-07	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-06-21	Not Related	None
79	Female	Yes	Yes	2018-02-22	2018-10-18	Disease progression	One tablet -50 mg	Respiratory, thoracic and mediastinal disorders	Lung disorder	2018-06-22	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-07-06	Not Related	None
79	Female	Yes	Yes	2018-02-22	2018-10-18	Disease progression	One tablet -50 mg	Nervous system disorders	Parkinsonism	2018-06-22	Severe	New/ Prolonged hospitalization	Not recovered/ not resolved		Not Related	None
79	Female	Yes	Yes	2018-02-22	2018-10-18	Disease progression	One tablet -50 mg	Infections and infestations	Lung infection	2018-11-01	Severe	Fatal	Fatal		Not Related	None
64	Male	No	Yes	2017-02-23	2017-06-18	Other - suicide	One tablet -50 mg	Psychiatric disorders	Completed suicide	2017-06-18	Severe	Fatal	Fatal		Unlikely	Drug permanentl y interrupted
77	Female	Yes	No	2017-03-10	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complicatio ns	Upper limb fracture	2018-01-25	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-01-30	Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
64	Female	Yes	Yes	2017-04-25	Ongoing		One tablet -50 mg	Vascular disorders	Hypertension	2017-11-21	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-11-30	Possible	None
64	Female	Yes	Yes	2017-04-25	Ongoing		One tablet -50 mg	Psychiatric disorders	Anxiety	2017-11-21	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-11-30	Possible	None
64	Female	Yes	No	2017-01-17	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Femur fracture	2017-05-14	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-05-22	Not Related	None
80	Male	Yes	No	2017-07-07	2017-07-21	Disease progression	One tablet -50 mg	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Prostate cancer	2017-08-21	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-08-24	Not Related	None
81	Female	Yes	No	2017-12-05	Ongoing		One tablet -50 mg	Infections and infestations	Retroperitoneal abscess	2018-06-18	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-11-16	Not Related	None
81	Male	Yes	No	2017-04-21	Ongoing		One tablet -50 mg	Cardiac disorders	Myocardial infarction	2018-01-30	Severe	Life threatening	Recovered/ resolved	2018-02-05	Not Related	None
89	Male	Yes	Yes	2017-10-09	Ongoing		One tablet -50 mg	Infections and infestations	Lung infection	2018-07-01	Severe	Fatal	Fatal		Not Related	None
85	Female	Yes	No	2017-12-16	Ongoing		One tablet -50 mg	Vascular disorders	Hypotension	2018-12-05	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-12-14	Not Related	None
86	Male	Yes	Yes	2018-03-22	Ongoing		One tablet -50 mg	Nervous system disorders	Somnolence	2018-05-12	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-06-NK	Not Related	Dosage reduced
86	Male	Yes	Yes	2018-03-22	Ongoing		One tablet -50 mg	Skin and subcutaneous tissue disorders	Decubitus ulcer	2018-05-19	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2019-02-NK	Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
86	Male	Yes	Yes	2018-03-22	Ongoing		One tablet -50 mg	Psychiatric disorders	Confusional state	2018-05-12	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-10-NK	Not Related	Dosage reduced
73	Female	Yes	Yes	2017-09-05	Ongoing		One tablet -50 mg	Psychiatric disorders	Anxiety	2017-09-11	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-09-21	Unlikely	None
73	Female	Yes	Yes	2017-09-05	Ongoing		One tablet -50 mg	Nervous system disorders	Neurological symptom	2018-04-23	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-05-04	Unlikely	None
73	Female	Yes	Yes	2017-09-05	Ongoing		One tablet -50 mg	General disorders and administration site conditions	Treatment noncompliance	2017-09-11	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-09-21	Unlikely	None
73	Female	Yes	Yes	2017-09-05	Ongoing		One tablet -50 mg	Psychiatric disorders	Hallucination, visual	2018-04-23	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-05-04	Unlikely	None
73	Female	Yes	Yes	2017-09-05	Ongoing		One tablet -50 mg	Psychiatric disorders	Depression	2017-09-11	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-11-21	Unlikely	None
69	Female	Yes	Yes	2018-02-23	Ongoing		One tablet -50 mg	Musculoskeletal and connective tissue disorders	Back pain	2018-02-23	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-03-06	Not Related	None
83	Male	Yes	Yes	2018-05-30	Ongoing		One tablet -50 mg	Infections and infestations	Lung infection	2019-02-08	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2019-02-25	Not Related	None
79	Female	Yes	Yes	2018-04-03	Ongoing		One tablet -50 mg	Nervous system disorders	Presyncope	2018-06-11	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-06-11	Unlikely	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
71	Male	Yes	No	2018-04-06	2018-08-20	Other - mesenteric infarction and cardiac arrest and death on the 20/08/2018 in intensive care	One tablet -50 mg	Gastrointestinal disorders	Intestinal ischaemia	2018-08-09	Severe	Fatal	Fatal		Unlikely	Drug permanently interrupted
71	Male	Yes	No	2018-04-06	2018-08-20	Other - mesenteric infarction and cardiac arrest and death on the 20/08/2018 in intensive care	One tablet -50 mg	Cardiac disorders	Cardiac arrest	2018-08-20	Severe	Fatal	Fatal		Unlikely	Drug permanently interrupted
71	Male	Yes	No	2018-04-06	2018-08-20	Other - mesenteric infarction and cardiac arrest and death on the 20/08/2018 in intensive care	One tablet -50 mg	Metabolism and nutrition disorders	Dehydration	2018-07-04	Severe	Fatal	Fatal		Unlikely	Drug permanently interrupted
71	Male	Yes	No	2018-04-06	2018-08-20	Other - mesenteric infarction and cardiac arrest and death on the 20/08/2018 in intensive care	One tablet -50 mg	Infections and infestations	Sepsis	2018-07-04	Severe	Fatal	Fatal		Unlikely	Drug permanently interrupted
65	Female	Yes	No	2017-02-11	Ongoing		One tablet -50 mg	Infections and infestations	Influenza	2018-01-13	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-01-20	Not Related	None
68	Female	Yes	No	2017-03-08	Ongoing		One tablet -50 mg	Ear and labyrinth disorders	Vertigo positional	2017-04-25	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2017-04-26	Unlikely	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
67	Male	Yes	Yes	2017-11-08	2018-11-21	Adverse reaction	One tablet -50 mg	Nervous system disorders	Cognitive disorder	2018-11-20	Moderate	Persistent/ Significant disability/ incapacity	Not recovered/ not resolved		Possible	Drug permanently interrupted
74	Female	Yes	Yes	2017-10-04	2017-10-15	Adverse reaction	One tablet -50 mg	Injury, poisoning and procedural complications	Femoral neck fracture	2018-08-07	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-09-NK	Not Related	None
74	Female	Yes	Yes	2017-10-04	2017-10-15	Adverse reaction	One tablet -50 mg	Injury, poisoning and procedural complications	Fall	2018-08-07	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-08-07	Not Related	None
74	Female	Yes	Yes	2017-10-04	2017-10-15	Adverse reaction	One tablet -50 mg	Nervous system disorders	Dyskinesia	2018-08-15	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-10-09	Not Related	None
76	Female	Yes	Yes	2017-11-03	2018-02-23	Adverse reaction	One tablet -50 mg	Psychiatric disorders	Hallucination	2018-02-18	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-05-29	Possible	Drug permanently interrupted
76	Female	Yes	Yes	2017-11-03	2018-02-23	Adverse reaction	One tablet -50 mg	Nervous system disorders	Dyskinesia	2018-02-13	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-05-29	Possible	Drug permanently interrupted
52	Male	No	No	2018-03-01	2018-12-16	Patient choice	One tablet -50 mg	Gastrointestinal disorders	Incarcerated inguinal hernia	2019-01-18	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2019-01-NK	Not Related	None
71	Female	Yes	No	2017-10-28	2018-06-06	Other - unknown	One tablet -50 mg	Cardiac disorders	Acute myocardial infarction	2018-04-07	Moderate	Other important medical event	Recovered/ resolved	2018-04-10	Not Related	None
71	Female	Yes	No	2017-10-28	2018-06-06	Other - unknown	One tablet -50 mg	Psychiatric disorders	Suicide attempt	2018-04-14	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-04-18	Unlikely	None
71	Female	Yes	No	2017-10-28	2018-06-06	Other - unknown	One tablet -50 mg	Psychiatric disorders	Suicidal ideation	2018-06-06	Severe	New/ Prolonged hospitalization	Recovering /resolving		Unlikely	NK

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
75	Male	Yes	No	2018-01-18	2018-12-29	Disease progression	One tablet -50 mg	Infections and infestations	Pneumonia	2018-10-07	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-10-13	Not Related	None
75	Male	Yes	No	2018-01-18	2018-12-29	Disease progression	One tablet -50 mg	Infections and infestations	Escherichia sepsis	2019-01-05	Severe	Fatal	Fatal		Not Related	None
75	Male	Yes	No	2018-01-18	2018-12-29	Disease progression	One tablet -50 mg	Infections and infestations	Escherichia sepsis	2018-11-14	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-11-23	Not Related	None
75	Male	Yes	No	2018-01-18	2018-12-29	Disease progression	One tablet -50 mg	General disorders and administration site conditions	Pyrexia	2018-12-03	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-12-17	Not Related	None
75	Female	No	No	2018-03-14	Ongoing		One tablet -50 mg	Infections and infestations	Urosepsis	2018-06-06	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-06-22	Not Related	None
75	Female	No	No	2018-03-14	Ongoing		One tablet -50 mg	Infections and infestations	Clostridium difficile colitis	2018-07-03	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-07-11	Not Related	None
84	Male	Yes	No	2017-02-23	2017-05-03	Adverse reaction	One tablet -50 mg	General disorders and administration site conditions	Death	2018-01-01	Severe	Fatal	Fatal		Not Related	None
77	Male	Yes	No	2017-03-11	Ongoing		One tablet -50 mg	Infections and infestations	Urinary tract infection	2018-02-01	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-02-12	Not Related	None
57	Male	No	No	2017-08-23	2018-04-25	Other - Deep brain stimulation	One tablet -50 mg	Injury, poisoning and procedural complications	Femoral neck fracture	2017-10-12	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-10-25	Not Related	None
67	Male	Yes	Yes	2017-11-05	Ongoing		One tablet -50 mg	Nervous system disorders	Epilepsy	2018-10-05	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-10-05	Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
88	Female	Yes	Yes	2017-11-15	Ongoing		One tablet -50 mg	Nervous system disorders	Cerebrovascular disorder	2018-03-24	Moderate	New/ Prolonged hospitalization	Recovered/ resolved with sequelae	2018-03-29	Not Related	None
88	Female	Yes	Yes	2017-11-15	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Skin injury	2018-07-19	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-08-24	Not Related	None
71	Male	Yes	No	2018-02-04	2018-04-20	Adverse reaction	One tablet -50 mg	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Leukaemia recurrent	2018-04-09	Moderate	Other important medical event	Recovered/ resolved	2018-09-27	Not Related	None
80	Male	Yes	Yes	2016-06-24	Ongoing		One tablet -50 mg	Surgical and medical procedures	Hernia repair	2017-04-04	Moderate	Other important medical event	Recovered/ resolved	2017-04-07	Not Related	None
76	Male	Yes	Yes	2018-01-09	2018-02-26	Patient choice	One tablet -50 mg	Nervous system disorders	Cerebral infarction	2018-06-07	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-11-30	Unlikely	None
79	Male	Yes	Yes	2018-01-17	2018-06-10	Other - Hospitalization	One tablet -50 mg	Injury, poisoning and procedural complications	Brain contusion	2018-05-11	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-07-06	Not Related	None
79	Male	Yes	Yes	2018-01-17	2018-06-10	Other - Hospitalization	One tablet -50 mg	Injury, poisoning and procedural complications	Upper limb fracture	2018-05-11	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-07-06	Not Related	None
79	Male	Yes	Yes	2018-01-17	2018-06-10	Other - Hospitalization	One tablet -50 mg	Injury, poisoning and procedural complications	Pelvic fracture	2018-05-11	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-07-06	Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
79	Male	Yes	No	2017-05-11	2017-05-14	Adverse reaction	One tablet -50 mg	Nervous system disorders	Cerebrovascular accident	2017-09-30	Moderate	New/ Prolonged hospitalization	Recovering /resolving		Not Related	None
76	Male	Yes	Yes	2017-08-02	2017-12-12	Patient choice	One tablet -50 mg	Nervous system disorders	Syncope	2017-09-21	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-09-23	Not Related	None
76	Male	Yes	Yes	2017-08-02	2017-12-12	Patient choice	One tablet -50 mg	Psychiatric disorders	Hallucination	2017-12-04	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-12-06	Not Related	None
76	Male	Yes	Yes	2017-08-02	2017-12-12	Patient choice	One tablet -50 mg	Injury, poisoning and procedural complications	Hip fracture	2018-03-21	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-03-29	Not Related	None
76	Male	Yes	Yes	2017-08-02	2017-12-12	Patient choice	One tablet -50 mg	Infections and infestations	Pneumonia	2018-05-03	Severe	New/ Prolonged hospitalization	NK		Not Related	None
76	Male	Yes	Yes	2017-08-02	2017-12-12	Patient choice	One tablet -50 mg	Psychiatric disorders	Delirium	2018-05-05	Severe	New/ Prolonged hospitalization	NK		Not Related	None
73	Male	Yes	No	2017-11-14	Ongoing		One tablet -50 mg	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Sarcoma of skin	2017-12-04	Severe	Life threatening	NK		Unlikely	None
69	Male	No	No	2018-04-26	2018-08-23	Adverse reaction	One tablet -50 mg	General disorders and administration site conditions	Pain	2018-11-12	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-11-15	Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
78	Male	Yes	Yes	2016-09-28	Ongoing		One tablet -50 mg	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Lipoma	2016-12-27	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2016-12-29	Not Related	None
87	Female	Yes	Yes	2016-09-23	Ongoing		One tablet -50 mg	Respiratory, thoracic and mediastinal disorders	Chronic obstructive pulmonary disease	2016-12-23	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2017-01-04	Unlikely	None
87	Female	Yes	Yes	2016-09-23	Ongoing		One tablet -50 mg	Social circumstances	Immobile	2017-03-15	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-04-06	Unlikely	None
55	Male	Yes	Yes	2016-11-11	2017-03-22	Other - Medical decision	One tablet -50 mg	Infections and infestations	Infection	2016-11-22	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2016-12-22	Not Related	None
80	Female	Yes	Yes	2017-01-21	Ongoing		One tablet -50 mg	Nervous system disorders	Movement disorder	2017-08-01	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2017-08-03	Not Related	None
80	Female	Yes	Yes	2017-01-21	Ongoing		One tablet -50 mg	General disorders and administration site conditions	Condition aggravated	2017-08-01	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2017-08-03	Not Related	None
80	Female	Yes	Yes	2017-01-21	Ongoing		One tablet -50 mg	Respiratory, thoracic and mediastinal disorders	Sleep apnoea syndrome	2017-07-18	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2017-07-20	Not Related	None
66	Female	Yes	Yes	2017-07-07	Ongoing		One tablet -50 mg	General disorders and administration site conditions	Therapeutic response shortened	2018-02-13	Mild	New/ Prolonged hospitalization	Recovering /resolving		Unlikely	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
66	Female	Yes	Yes	2017-07-07	Ongoing		One tablet -50 mg	General disorders and administration site conditions	Condition aggravated	2018-02-13	Mild	New/ Prolonged hospitalization	Recovering /resolving		Unlikely	None
77	Male	Yes	Yes	2017-12-22	Ongoing		One tablet -50 mg	Nervous system disorders	Movement disorder	2018-10-08	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2018-10-16	Unlikely	None
68	Male	Yes	No	2017-07-15	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Spinal compression fracture	2018-01-18	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-05-NK	Not Related	None
74	Male	Yes	No	2018-03-02	Ongoing		One tablet -50 mg	Psychiatric disorders	Delirium	2018-08-22	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-09-02	Not Related	None
75	Female	Yes	No	2018-03-27	2018-04-07	Other - no oral medication could be administered due to intubation (see SAE Pneumonia)	One tablet -50 mg	Infections and infestations	Pneumonia	2018-04-06	Severe	Fatal	Fatal		Not Related	Drug permanently interrupted
64	Male	No	Yes	2017-07-13	Ongoing		One tablet -50 mg	Psychiatric disorders	Major depression	2017-11-06	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-12-02	Not Related	None
71	Male	Yes	Yes	2018-01-31	Ongoing		One tablet -50 mg	Nervous system disorders	Parkinsonism	2018-07-30	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-08-11	Not Related	None
68	Female	Yes	Yes	2017-04-03	Ongoing		One tablet -50 mg	Nervous system disorders	Parkinsonism	2017-08-16	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-08-24	Not Related	None
68	Female	Yes	Yes	2017-04-03	Ongoing		One tablet -50 mg	Nervous system disorders	Dementia with Lewy bodies	2017-10-11	Moderate	New/ Prolonged hospitalization	NK		Not Related	NK

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
76	Male	Yes	No	2017-04-11	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Limb injury	2017-10-17	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2017-10-18	Not Related	None
76	Male	Yes	No	2017-04-11	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Head injury	2017-10-17	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2017-10-18	Not Related	None
72	Male	Yes	No	2017-02-22	Ongoing		One tablet -50 mg	Cardiac disorders	Cardiomyopathy	2017-03-02	Mild	Other important medical event	Recovered/ resolved	2017-03-06	Not Related	None
72	Male	Yes	No	2017-02-22	Ongoing		One tablet -50 mg	Investigations	Colonoscopy	2017-04-05	Mild	Other important medical event	Recovered/ resolved	2017-04-07	Not Related	None
62	Female	Yes	No	2017-08-24	Ongoing		One tablet -50 mg	Respiratory, thoracic and mediastinal disorders	Respiratory failure	2018-02-14	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-02-23	Not Related	NK
62	Female	Yes	No	2017-08-24	Ongoing		One tablet -50 mg	Infections and infestations	Pneumonia	2018-02-14	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-02-23	Not Related	NK
61	Male	Yes	No	2017-10-13	Ongoing		One tablet -50 mg	Surgical and medical procedures	Toe amputation	2018-02-15	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-02-27	Not Related	None
69	Male	No	No	2017-03-01	2017-03-13	Patient choice	One tablet -50 mg	Surgical and medical procedures	Medical device implantation	2017-10-16	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-10-18	Not Related	None
87	Female	Yes	Yes	2017-11-30	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Hip fracture	2017-12-10	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-12-18	Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
71	Female	No	Yes	2017-07-13	Ongoing		One tablet -50 mg	Infections and infestations	Staphylococcal bacteraemia	2018-03-27	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-07-17	Not Related	None
71	Female	No	Yes	2017-07-13	Ongoing		One tablet -50 mg	Infections and infestations	Staphylococcal meningitis	2018-03-27	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-07-17	Not Related	None
71	Female	No	Yes	2017-07-13	Ongoing		One tablet -50 mg	Infections and infestations	Staphylococcal infection	2018-03-27	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-06-08	Not Related	None
71	Female	No	Yes	2017-07-13	Ongoing		One tablet -50 mg	Infections and infestations	Intervertebral discitis	2018-03-27	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-06-08	Not Related	None
76	Male	Yes	Yes	2017-06-15	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Fall	2017-08-15	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2017-09-07	Not Related	None
80	Female	Yes	Yes	2017-09-27	2018-04-09	Adverse reaction	One tablet -50 mg	Renal and urinary disorders	Acute kidney injury	2018-04-03	Severe	New/ Prolonged hospitalization	Recovered/ resolved with sequelae	2018-04-25	Unlikely	Drug permanentl y interrupted
78	Female	Yes	Yes	2017-04-25	2018-03-03	Other - Death	One tablet -50 mg	Respiratory, thoracic and mediastinal disorders	Respiratory failure	2018-03-02	Severe	Fatal	Fatal		Not Related	None
71	Female	Yes	Yes	2017-10-11	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Fibula fracture	2018-10-19	Severe	New/ Prolonged hospitalization	Recovering /resolving		Not Related	None
73	Male	Yes	No	2017-04-25	2018-05-17	Adverse reaction	One tablet -50 mg	Musculoskeletal and connective tissue disorders	Pain in extremity	2018-05-17	Moderate	Persistent/ Significant disability/ incapacity	Not recovered/ not resolved		Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
72	Male	Yes	Yes	2018-04-18	Ongoing		One tablet -50 mg	Cardiac disorders	Bifascicular block	2018-05-30	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-06-01	Not Related	None
60	Female	Yes	No	2017-05-17	2017-12-01	Adverse reaction	One tablet -50 mg	Psychiatric disorders	Psychotic disorder	2017-11-15	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-12-05	Unlikely	Drug permanently interrupted
71	Male	Yes	Yes	2017-05-31	2017-06-01	Other - Death	One tablet -50 mg	Nervous system disorders	Cerebrovascular disorder	2017-06-01	Severe	Fatal	Fatal		Not Related	None
64	Male	Yes	No	2017-06-30	Ongoing		One tablet -50 mg	Hepatobiliary disorders	Cholecystitis acute	2018-05-07	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-05-16	Not Related	None
61	Male	Yes	No	2017-12-14	Ongoing		One tablet -50 mg	Cardiac disorders	Cardiac failure	2018-05-20	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-05-24	Not Related	None
61	Male	Yes	No	2017-12-14	Ongoing		One tablet -50 mg	Surgical and medical procedures	Knee operation	2018-05-14	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-05-24	Not Related	None
54	Male	Yes	Yes	2017-09-27	Ongoing		One tablet -50 mg	Musculoskeletal and connective tissue disorders	Lumbar spinal stenosis	2017-12-01	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-12-05	Not Related	None
75	Female	Yes	Yes	2017-06-20	2017-12-08	Adverse reaction	One tablet -50 mg	Nervous system disorders	Cerebrovascular accident	2018-02-25	Severe	Fatal	Fatal		Not Related	None
75	Female	Yes	Yes	2017-06-20	2017-12-08	Adverse reaction	One tablet -50 mg	Psychiatric disorders	Agitation	2017-11-22	Moderate	Persistent/ Significant disability/ incapacity	Not recovered/ not resolved		Possible	Drug permanently interrupted
67	Male	Yes	No	2018-02-23	Ongoing		One tablet -50 mg	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Tumour perforation	2019-02-05	Moderate	New/ Prolonged hospitalization	Recovering /resolving		Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
79	Male	Yes	No	2017-01-26	2017-05-21	Other - Lack of efficacy	One tablet -50 mg	Cardiac disorders	Acute coronary syndrome	2017-06-02	Severe	Fatal	Fatal		Not Related	None
81	Male	Yes	No	2017-05-24	2018-01-20	Other - Death	One tablet -100 mg	Cardiac disorders	Cardiac arrest	2018-01-20	Severe	Fatal	Fatal		Not Related	None
81	Male	Yes	No	2017-10-11	2018-06-10	Other - Death	One tablet -100 mg	Nervous system disorders	Cerebrovascular accident	2018-04-10	Severe	Life threatening	Not recovered/ not resolved		Not Related	None
81	Male	Yes	No	2017-10-11	2018-06-10	Other - Death	One tablet -100 mg	Respiratory, thoracic and mediastinal disorders	Pneumonia aspiration	2018-06-10	Severe	Fatal	Fatal		Not Related	None
52	Male	No	Yes	2017-08-10	Ongoing		One tablet -50 mg	Nervous system disorders	Dyskinesia	2017-08-11	Severe	Persistent/ Significant disability/ incapacity	Not recovered/ not resolved		Probable	None
60	Male	Yes	Yes	2018-01-26	2018-08-21	Disease progression	One tablet -50 mg	Psychiatric disorders	Suicide attempt	2018-08-21	Severe	New/ Prolonged hospitalization	Recovering /resolving		Unlikely	None
56	Female	No	No	2018-02-10	Ongoing		One tablet -100 mg	Surgical and medical procedures	Thyroid operation	2018-05-08	Moderate	Other important medical event	Recovered/ resolved	2018-05-09	Not Related	None
72	Male	No	Yes	2017-04-19	2017-10-25	Other - Hospitalization	One tablet -50 mg	Injury, poisoning and procedural complications	Hip fracture	2017-10-21	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-11-15	Not Related	Drug permanently interrupted
84	Female	Yes	Yes	2017-02-20	Ongoing		One tablet -50 mg	Infections and infestations	Respiratory tract infection	2017-06-30	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2017-07-04	Not Related	None
84	Female	Yes	Yes	2017-02-20	Ongoing		One tablet -50 mg	Infections and infestations	Respiratory tract infection	2017-09-18	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-09-22	Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
66	Male	Yes	No	2017-06-20	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Wrist fracture	2018-05-13	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-05-16	Not Related	None
66	Male	Yes	No	2017-06-20	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Radius fracture	2018-05-13	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-05-16	Not Related	None
58	Female	Yes	Yes	2017-10-17	2018-02-19	Adverse reaction	One tablet -100 mg	Injury, poisoning and procedural complications	Femur fracture	2018-05-01	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-09-01	Unlikely	Drug permanentl y interrupted
67	Male	Yes	Yes	2017-06-16	Ongoing		One tablet -50 mg	Cardiac disorders	Myocardial infarction	2017-08-10	Severe	Other important medical event	Recovered/ resolved	2017-08-15	Not Related	None
53	Male	Yes	No	2017-06-10	Ongoing		One tablet -50 mg	Cardiac disorders	Prinzmetal angina	2018-05-28	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-05-30	Unlikely	None
73	Male	Yes	Yes	2017-06-22	Ongoing		One tablet -50 mg	Infections and infestations	Pneumonia bacterial	2017-08-29	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-09-11	Not Related	None
72	Male	Yes	No	2017-06-20	Ongoing		One tablet -50 mg	Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	2018-02-20	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-03-01	Not Related	None
53	Female	Yes	Yes	2017-02-15	Ongoing		One tablet -50 mg	Surgical and medical procedures	Cholecystectomy	2017-07-10	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2017-07-11	Not Related	None
74	Female	Yes	No	2017-09-25	2017-10-15	Adverse reaction	One tablet -50 mg	Cardiac disorders	Atrioventricular block complete	2018-03-26	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-03-26	Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
82	Male	Yes	No	2017-12-15	Ongoing		One tablet -50 mg	Hepatobiliary disorders	Bile duct stone	2018-06-10	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-07-26	Not Related	None
82	Male	Yes	No	2017-12-15	Ongoing		One tablet -50 mg	Hepatobiliary disorders	Cholecystitis acute	2018-08-05	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-08-13	Not Related	None
65	Female	Yes	Yes	2018-02-26	Ongoing		One tablet -50 mg	Musculoskeletal and connective tissue disorders	Pain in extremity	2018-10-02	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-10-06	Not Related	None
79	Female	Yes	Yes	2017-05-17	2018-04-04	Other - Death	One tablet -50 mg	Respiratory, thoracic and mediastinal disorders	Pleural effusion	2017-11-17	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-11-24	Not Related	None
79	Female	Yes	Yes	2017-05-17	2018-04-04	Other - Death	One tablet -50 mg	Cardiac disorders	Cardiac failure	2018-04-02	Severe	Fatal	Fatal		Not Related	Drug permanently interrupted
38	Male	No	Yes	2018-03-13	2018-10-01	Adverse reaction	One tablet -50 mg	Social circumstances	Gambling	2018-05-31	Severe	Persistent/ Significant disability/ incapacity	Recovered/ resolved	2018-08-17	Unlikely	Drug permanently interrupted
80	Male	Yes	No	2017-07-20	Ongoing		One tablet -100 mg	Infections and infestations	Respiratory tract infection	2018-03-16	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-03-23	Not Related	None
61	Male	Yes	Yes	2018-01-17	Ongoing		One tablet -100 mg	Injury, poisoning and procedural complications	Toxicity to various agents	2018-10-25	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-11-07	Not Related	Drug temporarily interrupted
74	Male	Yes	No	2017-09-19	2018-11-02	Patient choice	One tablet -50 mg	Infections and infestations	Cellulitis	2017-09-21	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-10-21	Not Related	None
69	Female	Yes	No	2017-05-01	2017-07-03	Other - Hospitalization	One tablet -50 mg	Infections and infestations	Pneumonia	2017-07-15	Severe	Fatal	Fatal		Not Related	Drug permanently interrupted

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
77	Male	Yes	No	2018-03-22	2018-04-20	Other - Medical decision	One tablet -50 mg	Infections and infestations	Lower respiratory tract infection	2019-02-10	Severe	Fatal	Fatal		Not Related	None
76	Male	Yes	No	2017-08-10	2018-03-26	Other - Death	One tablet -50 mg	Gastrointestinal disorders	Duodenal ulcer perforation	2018-03-23	Severe	Fatal	Fatal		Unlikely	Drug permanently interrupted
69	Male	Yes	Yes	2018-02-19	2018-05-21	Adverse reaction	One tablet -50 mg	Nervous system disorders	Dyskinesia	2018-05-21	Mild	Other important medical event	NK		Probable	Drug permanently interrupted
61	Female	No	No	2018-04-09	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Femoral neck fracture	2018-10-13	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-12-03	Not Related	None
63	Female	Yes	No	2016-10-10	Ongoing		One tablet -50 mg	Cardiac disorders	Atrial tachycardia	2017-01-07	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-06-23	Unlikely	Drug temporarily interrupted
68	Male	Yes	Yes	2017-05-22	2017-08-10	Adverse reaction	One tablet -50 mg	General disorders and administration site conditions	Pyrexia	2017-08-01	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-11-NK	Unclassifiable	Drug permanently interrupted
80	Male	Yes	No	2017-01-30	Ongoing		One tablet -50 mg	Respiratory, thoracic and mediastinal disorders	Bronchial disorder	2017-06-29	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2017-06-29	Not Related	None
67	Female	Yes	No	2017-05-31	Ongoing		One tablet -50 mg	Nervous system disorders	Morton's neuralgia	2017-06-12	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-06-13	Not Related	None
65	Female	Yes	No	2017-12-21	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Hip fracture	2018-04-02	Moderate	New/ Prolonged hospitalization	Recovering /resolving		Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
62	Male	Yes	No	2017-01-12	Ongoing		One tablet -50 mg	Musculoskeletal and connective tissue disorders	Intervertebral disc protrusion	2017-07-01	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-09-NK	Not Related	None
71	Female	Yes	Yes	2017-05-05	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Anaemia postoperative	2017-07-07	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-02-NK	Not Related	None
51	Male	Yes	No	2017-04-13	Ongoing		One tablet -50 mg	Surgical and medical procedures	Deep brain stimulation	2018-02-20	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-02-27	Not Related	None
60	Female	Yes	Yes	2017-01-10	Ongoing		One tablet -50 mg	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Malignant melanoma	2017-11-15	Severe	Other important medical event	NK		Unlikely	None
55	Male	Yes	No	2017-05-25	2017-10-27	Adverse reaction	One tablet -50 mg	Infections and infestations	Urinary tract infection	2017-07-10	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-07-20	Not Related	None
55	Male	Yes	No	2017-05-25	2017-10-27	Adverse reaction	One tablet -50 mg	Infections and infestations	Diarrhoea infectious	2017-07-10	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-07-20	Not Related	None
55	Male	Yes	No	2017-05-25	2017-10-27	Adverse reaction	One tablet -50 mg	Infections and infestations	Urinary tract infection	2017-08-09	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-09-04	Not Related	None
78	Male	No	Yes	2017-06-26	Ongoing		One tablet -50 mg	Respiratory, thoracic and mediastinal disorders	Pneumonia aspiration	2018-05-26	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2018-08-NK	Not Related	None
76	Male	Yes	No	2017-05-25	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Fall	2017-11-20	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-11-29	Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
76	Male	Yes	No	2017-05-25	Ongoing		One tablet -50 mg	Nervous system disorders	Subarachnoid haemorrhage	2017-11-20	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-11-29	Not Related	None
82	Female	Yes	Yes	2017-05-23	Ongoing		One tablet -50 mg	Gastrointestinal disorders	Gastric perforation	2018-02-11	Severe	New/ Prolonged hospitalization	Recovered/ resolved with sequelae	2018-02-12	Not Related	Drug temporarily interrupted
67	Male	Yes	No	2017-06-27	Ongoing		One tablet -100 mg	Injury, poisoning and procedural complications	Femur fracture	2017-09-12	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-09-26	Not Related	Drug temporarily interrupted
67	Male	Yes	No	2017-02-17	Ongoing		One tablet -50 mg	Infections and infestations	Urinary tract infection	2018-01-25	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2018-03-18	Not Related	None
75	Male	Yes	No	2017-05-23	Ongoing		One tablet -50 mg	Nervous system disorders	Ischaemic stroke	2017-09-27	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-10-18	Not Related	None
76	Male	Yes	No	2017-10-03	2017-11-20	Adverse reaction	One tablet -50 mg	Cardiac disorders	Myocardial infarction	2017-12-01	Severe	Fatal	Fatal		Not Related	None
71	Male	Yes	No	2017-11-15	2018-03-12	Other - Adverse event	One tablet -50 mg	Psychiatric disorders	Suicide attempt	2018-03-11	Severe	Fatal	Fatal		Not Related	Drug permanentl y interrupted
78	Female	No	Yes	2017-06-13	2018-03-31	Adverse reaction	One tablet -50 mg	Psychiatric disorders	Hallucination, visual	2017-10-01	Mild	Other important medical event	Recovered/ resolved	2017-10-20	Probable	None
71	Male	No	Yes	2017-02-28	2018-01-29	Adverse reaction	One tablet -50 mg	Injury, poisoning and procedural complications	Humerus fracture	2018-01-29	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2018-01-29	Unlikely	Drug permanentl y interrupted
84	Male	Yes	No	2017-04-06	2017-05-22	Other - Adverse event	One tablet -50 mg	Infections and infestations	Pneumonia	2017-05-22	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-06-10	Not Related	Drug permanentl y interrupted

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
57	Male	No	Yes	2017-05-04	Ongoing		One tablet -50 mg	Infections and infestations	Urinary tract infection	2017-05-22	Mild	New/ Prolonged hospitalization	Recovered/ resolved	2017-05-28	Not Related	None
68	Male	Yes	Yes	2017-03-17	2017-07-14	Other - Death	One tablet -50 mg	General disorders and administration site conditions	Drowning	2017-07-14	Severe	Fatal	Fatal		Not Related	Drug permanently interrupted
75	Male	Yes	Yes	2017-04-18	Ongoing		One tablet -50 mg	Renal and urinary disorders	Urinary retention	2017-11-11	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-12-01	Unlikely	None
71	Male	Yes	Yes	2016-12-15	Ongoing		One tablet -50 mg	Musculoskeletal and connective tissue disorders	Muscle rigidity	2017-07-19	Moderate	New/ Prolonged hospitalization	Not recovered/ not resolved		Not Related	None
71	Male	Yes	Yes	2016-12-15	Ongoing		One tablet -50 mg	Infections and infestations	Pneumonia	2017-08-09	Severe	Fatal	Fatal		Not Related	None
67	Male	Yes	Yes	2016-10-20	Ongoing		One tablet -50 mg	Surgical and medical procedures	Nephrectomy	2017-05-10	Moderate	New/ Prolonged hospitalization	Not recovered/ not resolved		Not Related	Drug temporarily interrupted
67	Male	Yes	Yes	2016-10-20	Ongoing		One tablet -50 mg	Renal and urinary disorders	Nephrolithiasis	2017-07-19	Moderate	Other important medical event	Recovered/ resolved	2017-07-19	Not Related	None
75	Female	Yes	Yes	2017-01-10	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Femur fracture	2017-10-24	Moderate	New/ Prolonged hospitalization	NK		Not Related	None
77	Male	Yes	No	2017-05-06	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Hip fracture	2018-04-12	Severe	Other important medical event	Recovered/ resolved	2018-06-14	Not Related	None

Age	Gender	Relevant comorbidities (Yes/No)	Psychiatric comorbidities (Yes/No)	Safinamide start date	Safinamide end date /ongoing	Safinamide reason of discontinuation	Safinamide initial dose	System Organ Class	Preferred Term	SAE start date	Severity	Seriousness	Outcome	SAE date of resolution	Relation to Safinamide	Action taken
80	Female	No	No	2017-08-08	Ongoing		One tablet -50 mg	Nervous system disorders	Epilepsy	2018-04-18	Mild	Other important medical event	Recovered/ resolved	2018-04-18	Possible	None
79	Female	Yes	No	2017-03-10	Ongoing		One tablet -50 mg	Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Uterine cancer	2017-12-01	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-12-NK	Not Related	None
77	Female	No	Yes	2017-06-01	Ongoing		One tablet -50 mg	Injury, poisoning and procedural complications	Femur fracture	2017-07-17	Severe	New/ Prolonged hospitalization	Recovered/ resolved	2017-08-09	Not Related	None
82	Female	Yes	No	2017-11-30	2017-12-15	Other - Adverse event	One tablet -50 mg	Cardiac disorders	Cardiac failure	2017-12-15	Moderate	New/ Prolonged hospitalization	Recovered/ resolved	2017-12-22	Not Related	Drug permanentl y interrupted