18 December 2014
EMA/CHMP/393951/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Xadago

International non-proprietary name: safinamide

Procedure No. EMEA/H/C/002396/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Administrative information

Name of the medicinal product:	Xadago
Applicant:	Zambon SpA Via Lillo Del Duca, 10 20091 Bresso (Milan) ITALY
Active substance:	safinamide methanesulfonate
International Nonproprietary Name/Common Name:	safinamide
Pharmaco-therapeutic group (ATC Code):	Not yet assigned
Therapeutic indication:	Xadago is indicated for the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients.
Pharmaceutical form:	Film-coated tablet
Strengths:	50 mg and 100 mg
Route of administration:	Oral use
Packaging:	blister (PVC/PVDC/Alu)
Package sizes:	14 tablets, 28 tablets, 30 tablets, 90 tablets and 100 tablets

Table of contents

List of abbreviations

AADC Aromatic L-amino-acid decarboxylase

ACTH Adrenocorticotrophic hormone

ADL Activities of Daily Living

A:G Albumin:Globulin

ALDH Aldehyde dehydrogenase

ASMF Active substance master file

AUC Area under the serum concentration-time curve

AUC0-t Area under the serum concentration-time curve from time zero to time t

AUC0-∞ Area under the serum concentration-time curve from time zero to infinity

BCO Bilateral carotid occlusion

BCRP Breast Cancer Resistance Protein

BCS Biopharmaceutics classification system

BOCF Baseline Observation Carried Forwards

CHMP Committee for Medicinal Products for Human use

CL_{int} Intrinsic clearance

C_{max} Maximum serum concentration after a single dose

$C_{max,ss,u}$ Maximum unbound plasma concentration at steady-state

COMT Catechol-O-methyltransferase

CPP Critical process parameter

CQA Critical quality attribute

CRO Contract Research Organisation

DA Dopamine

DAT Dopamine Transporter

DDI Drug-drug interaction

DMSO *N*,*N*-Dimethylsulfoxide

EAE Experimental autoimmune encephalomyelitis

EC European Commission

ECG Electrocardiograph

EEG Electroencephalograph

EM Electron microscopy

ERG Electroretinography

ESPD Early stage Parkinson Disease

EU European Union

FAAH Human fatty acid amide hydrolase

FDA Food and Drug Administration

FMEA Failure mode effects analysis

GC Gas chromatography

GC-MS Gas chromatography mass spectrometry

GCP Good Clinical Practice

GLP Good Laboratory Practice

HDPE High density polyethylene

HLM Human liver microsomes

HPLC High performance liquid chromatography

5HT 5-hydroxytryptamine

ICH International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICP-MS Inductively coupled plasma mass spectrometry

ID_{50} Dose producing 50% inhibition

i.m. Intramuscular

i.p. Intraperitoneal

IR Infrared

i.v. Intravenous

KF Karl Fischer titration

LC-MS/MS Liquid chromatography/tandem mass spectrometry

LE Long Evans rat

LID L-dopa induced dyskinesia,

L-dopa Levodopa

LOCF Last Observation Carried Forward

LOQ Limit of quantification

LSPD Late stage Parkinson Disease

MAO-A Monoamine oxidase A

MAO-B Monoamine oxidase B

MDR Multidrug resistance

MES Maximal electroshock

MPP+ 1-methyl-4-phenylpyridinium

MPTP 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

MTD Maximum tolerated dose

NMR Nuclear magnetic resonance

NOAEL No-Observed-Adverse-Effect-Level

ONL Outer nuclear layer

OCT Optical Coherence Tomography

OC Observed Case

PD Parkinson's disease

PD-CRS Parkinson's Disease Cognitive Rating Scale

P-gp poly-glycoprotein

Ph. Eur. European Pharmacopoeia

PhIP 2-amino-1-methyl-6-phenylimidazole[4.5-b]pyridine

PK Pharmacokinetic

p.o. per os

PVC Polyvinyl chloride

PVDC Polyvinylidene chloride

QbD Quality by design

QOL Quality of Life

QSAR Quantitative structure-toxicity relationship

QTPP Quality Target Product Profile

RH Relative humidity

RIA Radio-immune assay

RNFL retinal nerve fiber layer

RDO Retrieved Drop Outs

s.c. Subcutaneous

SD Sprague Dawley rat

SD-OCT Spectral Domain Optical Coherence Tomography

SERT Serotonin Transporter

SmPC Summary of product characteristics

SPECT Single positron emission computed tomography

SR Safety Ratio

6-OHDA 6-hydroxydopamine

TDI Total daily intake

TEAE Treatment-Emergent Adverse Events

TH Tyrosine hydroxylase

t_{max} Time to the maximum observed serum concentration

UV Ultraviolet

V_{SS} Volume of distribution at steady state

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Zambon SpA submitted on 5 December 2013 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Xadago, through the centralised procedure falling within the Article 3(1) and point 3 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 22 July 2010.

The applicant applied for the following indication:

The treatment of patients with idiopathic Parkinson's disease (PD) as add-on therapy to:

- A single DA-agonist at a stable dose in early stage non-fluctuating patients, and
- A stable dose of L-dopa alone or in combination with other PD medications in mid- to late-stage fluctuating patients

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application. The applicant indicated that safinamide was considered to be a new active substance.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain tests or studies.

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision CW/1/2011 on the granting of a class waiver.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Applicant's request for consideration

New active Substance status

The applicant requested the active substance safinamide contained in the above medicinal product to be considered as a new active substance in itself, as the applicant claims that it is not a constituent of a product previously authorised within the Union.

Scientific Advice

The applicant received Scientific Advice from the CHMP on 16 November 2006 and 21 March 2013. The

Scientific Advice pertained to quality, non-clinical and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

1.2. Manufacturers

Manufacturer responsible for batch release

Catalent Germany Schorndorf GmbH
Steinbeisstrasse 2
D-73614 Schorndorf
Germany

1.3. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP:

Rapporteur: Johann Lodewijk Hillege Co-Rapporteur: Greg Markey

- The application was received by the EMA on 5 December 2013.
- The procedure started on 26 December 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 March 2014. The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 14 March 2014.
- PRAC RMP Advice and assessment overview, adopted by PRAC on 10 April 2014.
- During the meeting on 25 April 2014, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 25 April 2014.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 14 May 2014.
- The summary report of the GCP inspection carried out at the following sites: Chile on 31/03-04/04, Colombia on 7-10/04 and Peru 5-8/05/2014 was issued on 13 June 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant’s responses to the List of Questions to all CHMP members on 8 September 2014.
- PRAC RMP Advice and assessment overview, adopted on 11 September 2014.
- During the CHMP meeting on 25 September 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing and in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 20 October 2014.
- PRAC RMP Advice and assessment overview, adopted on 6 November 2014.
- During the CHMP meeting on 19 November 2014, outstanding issues were addressed by the applicant during an oral explanation before the CHMP.
- PRAC RMP Advice and assessment overview, adopted on 4 December 2014.
- During the meeting on 18 December 2014, the CHMP, in the light of the overall data submitted and

the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Xadago.

2. Scientific discussion

2.1. Introduction

Parkinson's disease (PD) is a major neurodegenerative disorder in which a progressive loss of nigrostriatal dopaminergic neurons leads to motor symptoms. In addition, several non-motor symptoms (e.g., fatigue, pain, anxiety, depression, sleep disturbances, constipation, and cognitive dysfunction) frequently occur prior to the occurrence of motor symptoms in PD, which may be due to dysregulation of other neurotransmitter systems in different brain areas. Glutamate and other neurotransmitters are believed to play important roles in the pathogenesis of primary symptoms, motor fluctuations, dyskinesias and possibly neuronal cell loss.

The understanding that PD is a syndrome of dopamine deficiency led to the introduction to clinical practice of L-dopa, a precursor of dopamine that crosses the blood brain barrier use of dopamine agonists and MAO- inhibitors B, the major dopamine metabolizing enzyme in man.

L-dopa is the most effective single therapy for PD. During the course of the disease motor fluctuations and dyskinesias occur. Whether this is related to long term L-dopa use, disease progression or both remains a matter of debate. In clinical practice, other dopaminergic treatments are used to reduce or delay the need for L-dopa therapy, or to improve the efficacy or moderate the side effects of L-dopa. E.g. dopamine agonists may be chosen in patients with a relatively early onset of PD (<60 years), to postpone the need for L-dopa. MAO-B inhibitors are use as monotherapy in early PD, or as adjunctive therapy to L-dopa, to improve motor functions.

Safinamide has been developed by Newron Pharmaceuticals SpA as adjunct therapy for the treatment of subjects with idiopathic Parkinson's disease (PD) as add-on to:

• a single DA-agonist at a stable dose in early-stage non-fluctuating subjects and

• a stable dose of L-dopa alone or in combination with other PD medications in mid- to late-stage fluctuating subjects

2.2. Quality aspects

2.2.1. Introduction

The finished product is presented as film-coated tablets containing 50 or 100 mg of safinamide as active substance.

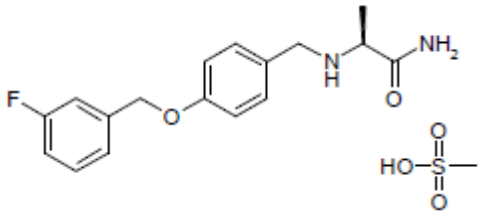
Other ingredients are: microcrystalline cellulose, crospovidone type A, magnesium stearate, colloidal anhydrous silica , hypromellose, polyethylene glycol 6000, titanium dioxide (E171), iron oxide red (E172) and mica (E555).

The product is available in PVC/PVDC/aluminium blister packs.

2.2.2. Active Substance

General information

The chemical name of safinamide is (+)-(*S*)-2-[[*p*-[(*m*-fluorobenzyl)oxy]benzyl]amino]propionamide monomethanesulfonate, and it has the following structure:



The structure of safinamide was unambiguously confirmed by ^{1}H and ^{13}C NMR spectroscopy, UV spectroscopy, IR spectroscopy, high resolution mass spectrometry, elemental analysis and single crystal X-ray diffraction.

Safinamide is a white to off-white, non-hygroscopic crystalline solid. It shows pH dependent solubility in aqueous buffers due to the secondary amine moiety, being soluble at acidic pH and practically insoluble at neutral pH. It is freely soluble in de-ionized water, methanol and DMSO but practically insoluble in non-polar organic solvents.

Safinamide is chiral and possesses a single stereogenic centre. Three crystalline forms are known. The anhydrous form selected for commercialisation is the most thermodynamically stable form, whilst the others are either not physiologically relevant or have very similar dissolution profiles.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

Manufacture, characterisation and process controls

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure. Safinamide is synthesized in three main steps using well defined starting materials with acceptable specifications. The single chiral centre originates in a starting material and the minor enantiomer is controlled in its specification.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and it was considered satisfactory.

The characterisation of the active substance and its impurities are in accordance with the EU guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised. Genotoxins used or generated in the process are controlled by the specifications of intermediates and are shown to be purged routinely by the manufacturing process. Heavy metals used in the process are purged and limited in the active substance specification. Polymorphic form and particle size distribution are controlled by the final crystallisation process.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are acceptable.

Specification

The active substance specification includes tests for appearance (visual inspection), identity (IR, HPLC, precipitation test for methylsulfonate counter-ion), assay (HPLC), related substances (HPLC), enantiomeric purity (HPLC), methanesulfonyl ester content (GC-MS), residual solvents (GC), heavy metals (in-house method), platinum (ICP-MS), residue on ignition (Ph. Eur.), water content (KF) and particle size distribution (laser diffraction). The absence of a test for polymorphic form is justified given the similar solubility of the other relevant forms.

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the ICH guidelines.

Analysis data on 16 batches of the active substance manufactured at pilot to production scale and used for stability, validation, qualification and clinical studies are provided. The results are within the specifications and consistent from batch to batch.

Stability

Stability data on six commercial scale batches of safinamide manufactured using the proposed commercial process stored in the packaging chosen to simulate that planned for production for up to 48 months under long term conditions (25 ºC / 60% RH), up to 12 months under intermediate conditions (30 ºC / 65% RH) and for up to 12 months under accelerated conditions (40 ºC / 75% RH) according to the ICH guidelines were provided. Photostability testing following the ICH guideline Q1B was also performed. Safinamide was also tested under stressed conditions including oxidation, heat, humidity, heat and humidity as well as high and low pH. The following parameters were tested: appearance, related substances (HPLC), assay (HPLC) and water content (KF). The analytical methods used were the same as for release and were stability indicating.

During the formal stability studies, no significant changes to any of the measured parameters, other than a minor increase in water content in relation to the relative humidity, but all samples were still within specification. Hydrolysis was observed at high pH (13) and some degradation under strong oxidation conditions was observed. The active substance is not sensitive to light, heat, or aqueous solution up to pH 10. The active substance deliquesces at high humidity but the long term data indicate that no specific storage condition is required.

The stability results indicate that the drug substance manufactured by the proposed supplier is sufficiently stable. The stability results justify the proposed retest period in the proposed container.

The applicant commits to the completion of all on-going stability studies under long term conditions up to the end of shelf-life.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Xadago is presented as orange, round, biconcave film-coated tablets embossed with "50" or "100" to distinguish the two strengths.

Pharmaceutical development was carried out along Quality by Design (QbD) principles. The quality target product profile (QTPP) was defined as an orally-available, immediate release film-coated tablet in easily distinguishable 50 and 100 mg strengths. The finished product should have a unique appearance, contain the requisite amount of active substance, be stable over the intended shelf-life, have acceptable mechanical properties, and comply with pharmacopoeial requirements. Critical quality attributes (CQAs) were identified as appearance, mass uniformity, hardness, disintegration and dissolution.

The active substance is highly soluble in acidic pH media but poorly soluble at pH 6.8 and is thus declared as BCS class II. The particle size of the active substance is therefore controlled in its specification to ensure a consistent dissolution profile.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SmPC.

Throughout the course of development, several iterations of dosage form were investigated from powder in bottle, to capsules, and finally to film-coated tablets. The manufacturing process and appearance of the tablets also changed over time. The process was successfully transferred to the proposed commercial

manufacturer. The switch from capsules to film-coated tablets was supported by *in vitro* dissolution data showing similar characteristics across the relevant pH range (1.2-6.8). The change in manufacturing process of the tablets was supported by a bioequivalence study. Further minor changes to formulation, appearance and manufacturing site were shown not to impact performance by comparison of dissolution profiles across the relevant pH range.

A risk assessment was carried out by failure mode effects analysis (FMEA), based on prior knowledge of the process to identify potential critical steps impacting finished product CQAs. A series of multivariate experiments was carried out on potentially critical steps, resulting in a design space for the roller compaction step. On transfer to the proposed commercial manufacturing site however, it was no longer possible to remain within the identified operating ranges. Therefore, no design space or regulatory flexibility is claimed in the dossier. Nonetheless, the operating ranges declared in the dossier are well-justified.

The discriminatory power of the dissolution method has been demonstrated in relation to batches manufactured by varying CPPs.

The primary packaging is PVC/PVDC/aluminium blister packs. The material complies with Ph. Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Manufacture of the product and process controls

The manufacturing process consists of four main steps including blending, granulation, compression and film-coating and is considered to be a standard process. Validation according to the validation scheme provided will be carried out before commercialisation. Despite the QbD principles applied during development, no design space or regulatory flexibility is claimed and the finished product is subject to final release testing.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for the production of Xadago film-coated tablets.

Product specification

The finished product release and shelf-life specifications include appropriate tests for this kind of dosage form and comprise tests for appearance (visual inspection), identification (HPLC, IR), assay (HPLC), related substances (HPLC), uniformity of dosage units (Ph. Eur.), dissolution (Ph. Eur.), water content (KF) and microbial limits (Ph. Eur.).

Batch analysis results provided for one commercial scale and two pilot scale batches of each proposed strength confirm the consistency of the manufacturing process and its ability to manufacture to the intended product specification. Batch analysis data on pilot and commercial scale batches of finished product, stored in different packaging, or made via old manufacturing processes, have been provided as supporting information.

Stability of the product

Stability data on one production scale and two pilot scale batches of finished product of each strength from the proposed manufacturer stored under long term conditions (25 ºC / 60% RH) for up to 12 months, under intermediate conditions (30 ºC / 65% RH and 30 ºC / 75% RH) for up to 12 months, and under accelerated conditions (40 ºC / 75% RH) for up to 6 months according to the ICH guidelines were provided. In addition, stability data on six batches of finished product of each strength from a different manufacturer, but using essentially the same process stored under long term conditions (25 ºC / 60% RH)

for up to 48 months, under intermediate conditions (30 ºC / 65% RH and 30 ºC / 75% RH) for up to 48 months, and under accelerated conditions (40 ºC / 75% RH) for up to 6 months were provided as supporting data. The tablets were stored in the primary packaging proposed for marketing. Samples were tested for appearance, assay, degradation products, dissolution, water content and microbial limits. Three batches of each strength from the different manufacturer were also tested for enantiomeric purity (chiral HPLC) and sum of methanesulfonate esters (GC-MS). In addition, the same three batches of each strength from the proposed commercial manufacturer were tested for hardness, enantiomeric purity, disintegration, polymorphic form and sum of methanesulfonate esters. The batches in question were used for stability, validation, clinical studies and registration.

No relevant change or trend to any of the measured parameters other than water content and assay was observed under the storage conditions investigated. Water content increases in relation to humidity, mainly during the first few months. Some variability in assay was observed for batches from the proposed commercial manufacturer, although no trend or evidence of degradation was detected. The applicant commits to investigate the source of this variability and update the dossier post-authorisation as required.

One batch per strength was exposed to light as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products. No significant trends were observed which demonstrates that the finished product tablets are not susceptible to photo-degradation.

Forced degradation studies were carried out on one batch of 50 mg tablets. Samples were exposed to light, heat, oxidant (H_2O_2), humidity, heat and humidity, and different pH levels (1, 7, 10, 13) in aqueous solution. Samples were tested for appearance, degradants, assay, enantiomeric purity, polymorphic form and where relevant, dissolution. Significant degradation was seen upon treatment with oxidant, at high pH, and at high heat and humidity. The product is resistant to racemization under all tested conditions. The analytical procedures were shown to be stability indicating.

Bulk stability testing was carried out on one batch of each strength stored under long term conditions in PE bags inside HDPE drums for 12 months. No trends other than a slight increase in water content were observed, justifying the proposed bulk holding period of 12 months.

Based on available stability data, the shelf-life as stated in the SmPC is acceptable.

Adventitious agents

No excipients derived from animal or human origin have been used.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

In the context of the obligation of the MAHs to take due account of technical and scientific progress, the CHMP recommends the following points for investigation:

The applicant should investigate variability of the finished product assay in batches manufactured at the proposed commercial manufacturing site and update the dossier as required.

2.3. Non-clinical aspects

2.3.1. Introduction

Safinamide is an alpha-aminoamide derivative, structurally unrelated to any other drug for treatment of Parkinson's disease.

The pharmacology program was divided into two phases. Initially safinamide was identified as a novel state and use-dependent blocker of voltage-gated sodium channels for potential use as an antiepileptic agent. Studies were carried out in standard pre-clinical seizure models. Subsequently, its reversible and selective Monoamine Oxidase B (MAO-B) inhibition, and interaction with glutamate release were identified and this led to its evaluation as an anti-parkinsonian agent as reduction in dopaminergic striatal transmission and hyperactivity of the glutamatergic pathway in the basal ganglia are implicated in the progression of PD. Safinamide has shown efficacy in preclinical models of PD as discussed further in this document.

Due to the inclusion of the MAO-B inhibition in the safinamide mechanisms, non-human primate models were preferred in the evaluation of PD-relevant pharmacology. In fact although some rodent models were employed in this phase, it was recognised that there are different neurochemical consequences of selective MAO-B inhibition in rodents compared to primates, since there is more widespread expression of MAO-A in the CNS of rodents than in humans and non-human primates. MAO-A can catalyse many of the same reactions as MAO-B but will not be inhibited by safinamide.

2.3.2. Pharmacology

2.3.2.1. Primary pharmacodynamic studies

Dopaminergic effects:

In vitro, safinamide showed approximately 5000 times higher selectivity for MAO-B than for MAO-A in rat brain homogenates and reversibly inhibited human platelet MAO-B with an IC50 of 9.3 nM (see Table 1 below). Differential sensitivity to inhibition was evident between brain and platelet MAO-B, however, with brain MAO-B IC50 values being almost 10 fold higher (i.e. less potent).

Table 1. In vitro MAO Inhibition in Rat and Human Tissues

	IC_{50} (µM)				
	MAO-A		MAO-B		
Tissue	Brain	Liver	Brain	Liver	Platelet
Rat	584[b]	~100[a]	0.098[b]	0.079[a]	not evaluated
Human	~80[a]	> 100[a]	0.079[a]	0.052[a]	0.064[a] 0.0093[b]

a: enzymatic inhibition studies in mitochondrial fractions prepared from rat and human liver, from human brain, and in human platelet-rich plasma (30-minute pre-incubation; *study 9650210*); b: enzymatic inhibition studies in rat brain mitochondria and in human platelet-rich plasma (*study 0601002*)

Safinamide is a reversible inhibitor of MAO-B as demonstrated in two sets of experiments using rat mitochondria. MAO-B inhibition by safinamide was not time-dependent; there was no significant difference between the IC50 obtained with or without pre-incubation.

Safinamide does not interact with enzymes involved in the levodopa metabolism AADC (aromatic L-amino-acid decarboxylase) and COMT (Catechol-O-methyltransferase), therefore it does not interfere with AADC and COMT inhibitors that are used in conjunction with levodopa to extend its duration of action and to provide benefits to PD patients suffering from motor fluctuations.

Safinamide differs from MAO-B inhibitors currently used for PD therapy (selegiline and rasagiline) in its mode of inhibition (non-covalent and reversible for safinamide, as compared with covalent and irreversible for selegiline and rasagiline) and by its additional activity at non-MAO-B targets.

In addition to MAO-B inhibition, drugs with pharmacological actions on several other molecular targets have been shown to enhance the efficacy of L-dopa on motor symptoms in Parkinson's disease and its animal models. To determine whether any of these targets might mediate safinamide's dopaminergic effects in animal models (see below) a number of specific studies were performed.

Stimulation of dopamine receptors types 1, 2 and/or 3 (D1, D2, D3) by dopamine agonists supplements the dopaminergic stimulation of neurons of the basal ganglia that is pathologically reduced in PD, and is the mechanism of action for several approved antiparkinsonian medications. Safinamide displayed no affinities for the different isoforms of D1, D2, D3, D4 and D5 dopamine receptor subtypes (-3% to 10% inhibition at 10 µM (study 0502001)).

In vivo, administration of 80 mg/kg to rats did not affect striatal dopamine metabolism, consistent with evidence that MAO-A primarily metabolises dopamine.

However dopaminergic effects of safinamide treatment on striatal neurochemistry have been demonstrated in primates, where dopamine is metabolised by MAO-B. Subchronic administration of safinamide (10-20 mg/kg/day for 13 weeks) produced an increase of dopamine levels in the striatum and a decrease of the DOPAC levels (dopamine metabolite). In parallel, MAO-B was significantly inhibited (study 0901003). Similar increase of dopamine levels in the striatum were measured after chronic treatment (8-20 mg/kg/day for 39 weeks, ES0714002). No changes in dopamine levels were found in the nucleus accumbens. The reason why nucleus accumbens dopamine levels were not affected was not discussed. The interaction with DA-releasing substances has not been addressed.

Binding to the dopamine and serotonin transporters (DAT, SERT) was evaluated both in recombinant systems and naïve tissues, and functional studies were performed to measure the safinamide concentrations producing inhibition of the monoamine reuptake. Overall, the *in vitro* lowest concentrations affecting the monoamine transporter functions approximated 10 µM. However an *in vivo* brain imaging study in baboons using the single positron emission computed tomography (SPECT) (study

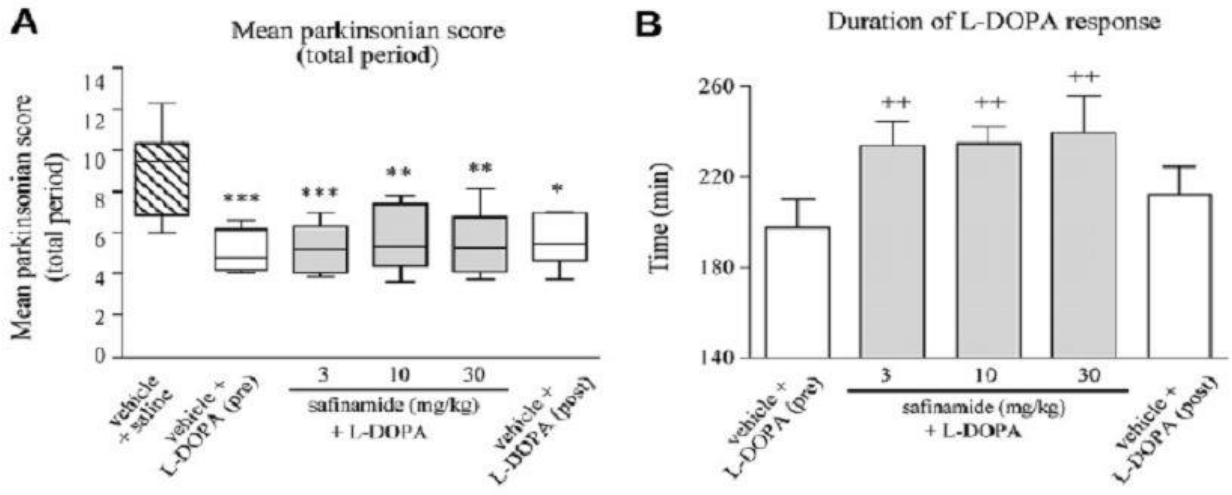
TANDD_invivo_2011.013 (MNI-Safinamide-2 REV 01), demonstrated that no displacement at either DAT or SERT sites occurs even when plasma concentrations reached a Cmax of 22850 ng/ml, significantly above the mean total plasma concentration of 1234 ng/ml measured in PD patients taking safinamide 100 mg/day dose.

In vivo, behavioural effects expected to be due to central MAO-B inhibition have been observed in the MPTP-lesioned macaque monkey disease model.

In Parkinson's disease patients, years of daily L-dopa therapy coupled with progressing neurodegeneration leads to the state in which each administration of L-dopa can be followed by a period of uncontrolled involuntary movements, termed L-dopa-induced dyskinesia (LID). Attempts to manage this side effect usually include restriction of L-dopa usage, resulting in less effective control of the cardinal parkinsonian symptoms. The neurochemical changes underlying the dyskinetic state are not completely understood but altered glutamate and endogenous opioid signalling have been implicated. In a well-accepted preclinical model of LID, macaque monkeys are treated with individually tailored doses of the dopamine neuron-selective toxin MPTP to induce neuron loss comparable with that occurring in mid-late stage PD patients. After several months' chronic treatment with L-dopa, a dyskinetic state is induced. (Jenner P. Nature Reviews Neuroscience 9, 665-677 (2008).

Safinamide, given in a range of doses po from 3, to 30 mg/kg to L-dopa treated MPTP-lesioned parkinsonian macaque monkeys, produced a significant increase in the duration of the anti-parkinsonian efficacy of L-dopa and maintained the anti-parkinsonian and locomotor intensity of the L-dopa effect. The extension of the L-dopa effect was maximal at any dose and in all experimental settings (single dose and semi-chronic administration), suggesting that the high affinity target MAO-B is involved in mediating the pro-dopaminergic effects (study TANDD_invivo_2011.009; Gregoire L et al. Parkinsonism Relat Disord. 2013 May;19(5) 508-14) (Figure 1below)).

Figure 1 Effect of safinamide added to L-dopa administered to MPTP monkeys as compared to L-dopa alone (pre and post safinamide) and vehicle



In an independent experiment in the same model 20 mg/kg safinamide administered orally one hour before L-dopa extended the L-dopa induced ON-time by 40 min, without modifying the antiparkinsonian and locomotor intensity of the L-dopa effect. (Study TANDD_invivo_2011.010; Gregoire L et al. Parkinsonism Relat Disord. 2013 May;19(5) 508-14).

Another study showed that, when administered for a week at 10 mg/kg BID in combination with L-Dopa in MPTP monkeys, safinamide maintained the antiparkinsonian and locomotor intensity of the L-dopa effect and increased the duration of the antiparkinsonian effect of L-dopa by more than half an hour; all these effects were maintained during the one-week treatment. In addition, the L-dopa motor effect started earlier after administration of L-dopa on the 7th day of chronic safinamide, likely due to the accumulation of safinamide over the week of administration (study TANDD_invivo_2011.011 (work plan 4); Gregoire L et al. Parkinsonism Relat Disord. 2013 May;19(5) 508-14).).

Intraperitoneal safinamide (10-40 mg/kg, 30 min before MPTP injection) completely prevented MPTP-induced neurotoxic effects in MPTP-treated (40 mg/kg sc for 2 days) C57 BL mice. Significant protection of nigral tyrosine hydroxylase (TH) positive neurons was found even when the compound was administered 4 h after MPTP. Safinamide (intraperitoneal 20 mg/kg) administered 15 days after MPTP significantly augmented (60% increase) the L-dopa induced elevation of striatal dopamine in mice.

Non-Dopaminergic effects:

In vitro, the properties of safinamide as a sodium (Na+) channel blocker were initially characterised in radioligand binding studies and in electrophysiology patch clamp studies performed in rat hippocampal and cortical neurons. Safinamide bound to voltage gated Na^+ channels (NaV) from rat brain membranes, and inhibited Na^+ currents in rat brain neurons, at low micromolar range and in a use-dependent manner, more potently than the anticonvulsants phenytoin and lamotrigine (study 970003; study 9750001; Salvati et al., J. Pharmac. Exp. Ther. 288:1151-1159, 1999).

In a further study on cells expressing recombinant sodium channels subtypes Nav.x (Nav 1.1 to Nav 1.8) it was demonstrated that safinamide displayed only modest selectivity (<5 fold) across the NaV subtypes under physiologically relevant stimulation. There was however a clear state-dependent effect, with a substantial difference in potency between resting and inactivated channels: IC50 values were decreased to a range between 1.6 and 4.9 μM under depolarized condition, suggesting safinamide preferentially bound to the inactivated state of the sodium channel. Of these channels, Nav 1.1-1.3 and NaV 1.6 are highly expressed in the brain.

Safinamide has been shown to inhibit calcium currents more potently than phenytoin and lamotrigine. This mechanism was theorised contribute to its non-dopaminergic and neuroprotective activity (study 9750001; Salvati et al 1999). Binding studies showed a weaker affinity of safinamide for calcium channels (<25% binding at the single concentration 10 μM) respect to sodium channels (67% binding at the single concentration 10 μM) (study 8060252). The potency of safinamide to inhibit electrical field stimulation (EFS)-induced intracellular calcium mobilisation (an effect due to sodium channels) was higher than the potency to inhibit K^+-induced calcium mobilisation (an effect due to calcium channels) (study 0604009).

Glutamate is released in a calcium and sodium-dependent manner in response to nerve terminal depolarisation. In rat hippocampal synaptosomes safinamide inhibited the release of glutamate and GABA (gamma-aminobutyric acid) induced by high K^+ (IC50 = 9.5 μM and 9.61 for the inhibition of glutamate and GABA release, respectively) (study 0203001-E).

In in vivo microdialysis studies in rats, safinamide has been shown to decrease veratridine (sodium channel activator)-stimulated hippocampal glutamate release without affecting basal glutamate release. The active dose was 30 mg/kg i.p. that would produce a free plasma concentration of 0.6 μM. this concentration overlaps with the range of free plasma concentrations (0.26μM - 0.77μM) reached in PD patients taking 100 mg/day dose. However, veratridine-induced glutamate release is an experimental condition not reflecting clinical practice and rat brain/plasma ratios of safinamide concentrations exceed those of primates. It is therefore uncertain if therapeutic doses safinamide would lead to clinically relevant effects on glutamate release in PD patients.

In vivo, in a model of L-dopa induced dyskinesia (LID) in MPTP-lesioned macaque monkeys, safinamide treatment caused a significant dose-dependent reduction in dyskinesia scores, concomitant with the extension in duration of relief from primary parkinsonian symptoms. Monkeys in the LID studies showed plasma levels in the range of the plasma concentrations found in the rat at the effective dose producing inhibition of the glutamate release, however, brain-blood ratios in monkeys were lower than in rodents. In a similar model in cynomolgus monkeys, however, an antidyskinetic effect was not confirmed.

"Wearing off" is a common treatment complication in PD, in which the duration of efficacy of a dose of L-dopa on motor symptoms is reduced, after a long period, usually years, of daily L-dopa therapy. In a model of this phenomenon in 6-OHDA unilaterally lesioned rats, rotations in response to a fixed dose of L-dopa are significantly reduced in number after 28 days of twice daily L-dopa administration. On day 29 the number of rotations was increased significantly when L-dopa was co-administered with 20 mg/kg safinamide i.p., or with the reference inhibitor of NMDA-type glutamate receptors MK-801 at 0.1 mg/kg i.p., compared to vehicle (refer to study ES0610005). It was speculated that this increase may not be due to MAO-B inhibition but instead could be due to non-dopaminergic mechanisms including interference with glutamate signalling.

The *tremulous jaw movement model*, is a rat model of parkinsonian tremor where repetitive vertical deflections of the lower jaw that resemble chewing, (but are not directed at a particular stimulus), can be pharmacologically induced by different agents such as DA antagonists, DA depletion, and cholinomimetics, and can be reversed by various antiparkinsonian drugs, including L-dopa, DA agonists, anticholinergics and adenosine A2A antagonists. Safinamide significantly reduced the number of tremulous jaw movements induced by galantamine, pilocarpine, and pimozide, with consistent effects across all three drugs at a dose range of 5.0–10.0 mg/kg i.p. Again, it was theorised that since MAO-B is not an important metabolic pathway for dopamine in the rat brain, it is likely that this effect on tremors may not be due to MAO-B inhibition but instead could be due to non-dopaminergic mechanisms including interference with glutamate signalling.

2.3.2.2. Secondary pharmacodynamic studies

Efficacy has also been documented in several preclinical models of epilepsy. The maximal electroshock (MES) model is a validated pre-clinical test that is highly predictive of anticonvulsant activity, and has been demonstrated to identify drugs effective in the treatment of generalized seizures of the tonic–clonic (grand mal) type, that act by blocking sodium channels. The ED50s of safinamide in the MES test after oral treatment were 8.0 mg/kg in mice and 11.8 mg/kg in rats (study 9650206). The correspondent pharmacodynamically available brain concentrations that produce the anticonvulsant effect in the MES test are 2.5µM (mice) and 4µM (rats), that overlap with the concentrations required to produce state-dependent blockade of the sodium channels in vitro. Yet, clinically, anticonvulsive activity of safinamide was not proven, as only open label studies comparing with baseline where provided.

Exploratory studies

In comparative in vitro studies with safinamide and its R-enantiomer on the MAO enzymatic activity (study 2003-66A; Strolin Benedetti et al., 1995), it was shown that The (R)-enantiomer was approximately 3-10 times less potent as MAO-B inhibitor (0.34 - 1.77 µM in the two studies, respectively) and 3-7 times more potent as MAO-A inhibitor (42 - 50 µM in the two studies, respectively) respect to safinamide. This was also demonstrated ex vivo 1 h after oral administration of 1,5,10 and 60 mg/kg doses.

A study was conducted to see if safinamide had an effect on slowing the retinal degeneration in the Royal College of Surgeon (RCS) rat strain. The efficacy of Safinamide was evaluated in the RCS rat to determine if it could slow the progression of the natural retinal degeneration. The potency / efficacy to prevent or slow down the retinal degeneration were assessed by measuring retinal DNA levels. Safinamide (15 or 30 mg/kg ip) failed to prevent or slow the natural rate of retinal degeneration in RCS rats not exposed to a photic insult (study 1105005).

Safinamide was investigated in the Tail Suspension Test in the mouse to evaluate its potential antidepressant activity. Safinamide 10, 40 and 100 mg/kg po, administered 60 minutes before the test, did not affect the duration of immobility as compared with vehicle control group, suggesting that it does not display anxiolytic-like or antidepressant-like activity (study 00803006 (03.243/2.

2.3.2.3. Safety pharmacology programme

Safinamide has been evaluated in several studies investigating central nervous, cardiovascular, respiratory, renal and gastrointestinal systems. Moreover, in vitro safety pharmacological investigations were conducted to investigate potential off-target effects of safinamide on various cell receptors, ion channels, transporters and enzymes. In addition to the safety pharmacological characterisation of safinamide, all 3 main human metabolites of safinamide and the R-enantiomer of safinamide (drug impurity) were also investigated in in vitro studies.

Receptor Profiling

In *in vitro* receptor profiling studies, possible effects of safinamide, its main human metabolites NW-1153, NW-1689 and NW-1689 AG, as well as its R-enantiomer (drug impurity), were investigated on up to 299 potential human off-targets (studies 8920172, 8920174, 8920175, 8920177, 8920196, 8060252, 8920254, 8920256, 8920286, 8920316, 8920326, 1205014). It was stated that if an off-target was affected to more than 50% of control binding at a final concentration of 10 µM a functional follow-up assay was performed to clarify whether receptor binding was translated into functional action.

At 10 µM, safinamide inhibited the imidazoline 1 receptor (an anti-hypertensive target) by 73 %with no expected clinical relevance since the intended highest clinical dose is 22-fold below the test concentration used.

The imidazoline 2 receptor, known as an allosteric binding site for the MAO-B, was inhibited by safinamide, and its main human metabolites NW-1153 and NW-1689 with IC50s of 0.72 µM, 0.8 to 1.4 µM or higher than 100 µM, respectively. The imidazoline 2 receptor may contribute to an inhibition of MAO-B and thereby to an increase in arterial blood pressure, but it has to be noted that there was absence of any effects on arterial blood pressure in conscious dogs and monkeys in the various safety pharmacological and toxicological studies.

The muscarinic receptors, in particular M3 (IC50 = 0.25 µM), were also affected by safinamide. However, a follow-up functional study (study 8920196) revealed much lower potencies for M3- (EC50 > 10 µM) and M4- (EC50 > 30 µM) dependent increase in intracellular Ca^{2+} concentrations than expected from the ligand binding data which represent a human safety margin of at least x22 and x66, respectively.

Safinamide and its main human metabolite NW-1153 displaced specific ligand binding at sigma 1 and 2 receptors and that is why the possible functional consequence of the safinamide binding to the sigma 1 receptor was investigated by a guinea pig vas deferens bioassay (study 8920177). Safinaminde and its metabolites did not demonstrate an agonistic action in this model, but in contrast, an antagonistic action characterised by an inhibition of 14%, 41% and 74% was observed at 3, 10 or 30 µM safinamide, respectively. In one previous study in guinea pig vas deferens preparation safinamide had showed neither

agonistic nor antagonistic effects on sigma non–selective receptors (study 0806010). Taken together according to the data it was concluded that neither safinamide nor its main metabolites NW-1153 and NW-1689 are likely to provoke pronounced adverse effects via sigma 1- and 2- receptors at the mean free peak plasma concentration of 0.4 µM safinamide in patients after administration of the intended highest clinical dose of 100 mg/day.

Cardiovascular system (in vitro):

Safinamide (1, 10, 100 µM) decreased hERG current in a dose-related and reversible manner with an IC50 of 28.3 µM in GLP study 091104.NFS (x63 expected free plasma concentrations in humans administered the maximum proposed daily dose of 100 mg). In further studies, adequate safety margins were demonstrated for inhibition of ATP-dependent potassium channel Kir6.2/SUR2A (IC50 = 9.3 µM), the sodium channel Nav1.5 (phasic stimulation: IC50 = 34.1 µM, tonic stimulation: IC50 > 100 µM) and Kv4.3 (IC50 = 32.4 µM) by safinamide, and hence concluded to be of low clinical relevance. Results from three studies (study 1204014, study 100819.NFS and study 1204014) to investigate the potential inhibition of HCN4 (a pacemaker channel of the sinoatrial node), showed that it was unlikely that safinamide would inhibit the HCN4 ion channel at clinically relevant concentrations.

In canine Purkinje fibres, the action potential duration (APD) was shortened dose-dependently by safinamide at 3 µM and above. APD shortening was dependent on the stimulation rate and was largest at a low stimulation rate (0.33 Hz). At 3 µM the APD was shortened by 32, 28 and 24% for APD50, APD70 and APD90, respectively. At 30 µM these values were 89, 73 and 56%, respectively. In isolated guinea pig papillary muscles, the refractory period was reduced by -2.2 ± 0.8%, -7.5 ± 1.9%, and -18.8 ± 3.5%, at 3, 10, and 30µM, respectively. The force of contraction was reduced by -15.7 ± 8.5%, -50.3 ± 5.3%, and -76.2 ± 2.6%, at 3, 10, and 30µM, respectively.

At high concentration of 100 µM, a significant increase in ventricular conduction time and a prolongation of refractory period in rabbit ventricular strips, and a reduced spontaneous automaticity in rabbit right atria were observed. These effects were mostly reversible upon washout. (Study 7243-96-080) and at 100µM considered to occur at concentrations far exceeding that expected in the clinic.

Cardiovascular system (in vivo): Safinamide showed no significant effect on mean arterial blood pressure in conscious and anesthetised rats administered oral doses of 10, 30 or 100 mg/kg or intravenous bolus of 50 mg/kg safinamide (study 7243-97-016).

The potential effect of safinamide on the neuronal uptake of noradrenaline or on adrenoreceptors (study 2000-39) was investigated in the anesthetized rats. Safinamide had no effect on mean arterial blood pressure and did not affect the pressor response curve to noradrenaline.

In conscious rats a study was conducted to investigate the potential for an interaction between safinamide and tyramine (study 2001-42). The selective MAO-A inhibitor clorgyline was used as a positive reference standard at an oral dose of 5 mg/kg. Safinamide, unlike clorgyline, did not influence the effect of tyramine on arterial blood pressure, suggesting that it does not interact with dietary tyramine and is unlikely to cause the "cheese effect" in patients.

In conscious dogs after single oral administration, safinamide at 5 and 15 mg/kg did not cause any statistically significant effect on heart rate and mean arterial blood pressure. At the dose of 50 mg/kg safinamide induced a very slight but significant increase in mean and diastolic arterial pressure and a decrease in QT interval duration at 1 h after treatment. In a second study in conscious dogs, the slight increase in heart rate at 50 mg/kg ($p<0.05$ vs. 0 min and vs. control) and a slight and dose-dependent decrease in QT interval of the ECG between 10 and 240 minutes (at 30 mg/kg: $p<0.05$ vs. 0 min; at 50 mg/kg: $p<0.05$ vs.0 min and vs. control) was confirmed. However, no changes in arterial blood pressure,

respiratory rate, body temperature, saturation and blood parameters were observed. With regard to the high dose (50 mg/kg), total mean C_{max} of the S-enantiomer safinamide in dogs was 7-fold above that in humans. The total mean C_{max} values of the main metabolites NW-1153, NW-1689 and acyl glucuronide of NW-1689 in dogs were 19-, 32- or 6.7-fold, respectively, above the total mean C_{max} values in healthy volunteers after single oral administration of 100 mg safinamide /subject/day. With respect to the R-enantiomer of safinamide, a safety margin of at least 150-fold can be determined.

Safinamide caused mortality at high toxicological doses in cynomolgus monkeys (study 9750238). In an exploratory safety pharmacological evaluation in anesthetized and conscious monkeys, intraduodenal administration up to 240 mg/kg did not show any effect on heart rate, arterial blood pressure, ventricular dP/dt, ECG parameters and respiration. Intravenous infusion resulted in hypotension, decrease in dP/dt, and death of the animals starting from cumulative total doses of 113 to 171 mg/kg (corresponding to plasma concentrations of 37.3 - 57 µg/mL). Continuous intracisternal infusion of safinamide at total doses of 22.3 and 118.8 mg/animal had principally the same effects as the intravenous infusion but at much lower plasma concentration, i.e. 0.32 and 5.6 µg/mL, respectively.

The Table 2 below summarises the results obtained in this cardiovascular study and compares the routes, respiration status, and plasma concentrations of safinamide.

Table 2 Cardiovascular Study Results in Monkey

			At Time of Peak Hypotension		
Animal ID	Route	Curare/AssistedRespiration	Total Dose	Plasma Conc. (ng/mL)	Molarity
327	*iv*	No/No	146 mg/kg	41,600	1.04×10^{-4}
312	*iv*	No/No	123 mg/kg	37,300	0.94×10^{-4}
94	*iv*	No/No	171 mg/kg	57,000	1.43×10^{-4}
91	*iv*	Yes/Yes	113 mg/kg	39,013	0.98×10^{-4}
95	*ic*	Yes/Yes	119 mg	5,573	1.40×10^{-5}
288	*ic*	No/Yes	22.3 mg	320	8.04×10^{-7}

iv = intravenous, *ic* = intracisternal infusion

Respiratory: Single oral administration of up to 200 mg/kg safinamide and 30 mg/kg R-enanthiomer had no pathophysiologically relevant effects on any of the parameters evaluated in a respiratory study in rats (study GSP0010RF).

CNS: Irwin tests were conducted in mice (study 9750104 (858X) and rats (study 11.0016) and the rotarod test in mice (study 9650206) and rats (study n. 9650207). In rats, safinamide caused slight and dose-dependent sedative effects (decrease in activity and abdominal muscle tone) associated with mydriasis after oral treatment with 30 to 200 mg/kg. In general, these effects lasted up to 180 minutes after treatment.

Possible effects of single oral doses of 10, 100 or 400 mg/kg safinamide on cognitive function were investigated in rats by using the passive avoidance procedure (study 9650207). Safinamide did not impair passive avoidance up to the highest tested dose of 400 mg/kg per oral.

Renal function: Safinamide was given to conscious rats at single oral doses of 30, 100 or 300 mg/kg (study 9750236 (N856-Q1519)). No relevant effects were seen on renal function.

Gastrointestinal Function: Safinamide was given to conscious mice at single oral doses of 30, 100 or 300 mg/kg (study 9750274 (N859-Q1520)). No relevant effects on intestinal transit were seen.

2.3.2.4. Pharmacodynamic drug interactions

Effects on Aromatic L-amino-acid Decarboxylase (AADC) and Catechol-O-methyltransferase (COMT)

Safinamide, safinamide acid and N-dealkylated acid inhibited the rat brain AADC activity in the high µM range, with IC50s of 573, 94 and 97 µM, respectively. The rat liver AADC was not inhibited up to 600 µM. In the same experimental conditions, carbidopa, used as reference compound, inhibited the rat brain AADC activity with an IC50= 2 µM. (study 1205009).

In vitro, safinamide did not inhibit COMT activity at concentrations up to 10 µM (study 0504005).

The lack of pharmacodynamics drug interaction with COMT or AADC inhibitors was confirmed in vivo. When orally co-administered in rats, safinamide at 10 mg/kg with L-dopa (40 mg/kg) + carbidopa (10 mg/kg), or with L-dopa (40 mg/kg) + carbidopa (10 mg/kg) + entecapone (10 mg/kg) did not affect the L-dopa metabolism, as shown by absence of an increase in plasma levels of L-dopa and its metabolite 3-OMD (0405001(PR051740)) .

2.3.3. Pharmacokinetics

Pharmacokinetic studies

The pharmacokinetics of safinamide have been investigated *in vivo* in rat and monkey and to a more limited extent in mouse, rabbit, dog and mini-pig. The kinetics of safinamide and its major metabolites (NW-1153, NW1689 and NW-1689 glucuronide) were investigated after IV and/or oral administration with a single and/or repeated dose. In addition, repeated dose studies in which safinamide was co-administered with other commonly prescribed Parkinson medications such as levodopa/carbidopa and pramipexole had been performed.

Furthermore, *in vitro* studies investigating the absorption, plasma-protein binding, blood-to-plasma ratio, metabolism, transporters and potential drug interactions were performed with safinamide and in some cases with metabolites of safinamide.

2.3.3.1. Methods of analysis

HPLC methods

A HPLC method with fluorescence detection was developed for the quantification of safinamide in mouse, rat, and monkey plasma (studies METPK 149/95; FCE26743S/101i; METPK 110/94; 9550130). Intra- and inter-assay accuracy and precision were within the validation criteria (≤15% and ≤20% at LLOQ).

Exploratory mouse and monkey brain assays were developed in parallel with the plasma methods with a calibration curve of 20-4000 ng/g tissue, though these were not validated (studies METPK 149/95; METPK 150/95).

LC-MS/MS methods

LC-MS/MS methods have been subsequently developed for the quantification of safinamide in plasma of mice, rat, rabbit and monkey to support non-clinical development.

An analytical method was also developed for the analysis of safinamide in bile and urine to support non-clinical excretion studies with an LLOQ of 20 ng/mL in bile and 500 ng/mL in urine (study 98/01). Methods for quantification of safinamide, NW-1153 and NW-1689 were also developed in rat retinal tissue and fat to support toxicological investigations with LLOQs of 40 ng/g, 40 ng/g and 80 ng/g for safinamide,

NW-1153 and NW-1689 respectively (studies SOI0047 and SOI0051). Precision and accuracy were ≤15% for bile, urine, retinal tissue and fat tissue.

Some of the developed LC-MS/MS methods for safinamide in rat, rabbit and monkey plasma have been additionally validated for NW-1153 and NW-1689 (studies SOI0034; P004/05; P003/05; 0070/455; 0070/457; 0070/456; 8200377; and 8224857) while separate LC-MS/MS methods for detection of the NW-1689 glucuronide in rat and monkey plasma were developed. Furthermore, an analytical method was developed for the analysis of NW-1199 in rat and monkey plasma (studies 0070/470 and 0070/471). The LLOQ was 1 ng/mL in rat and monkey plasma. Precision and accuracy were ≤15%.

Analytical methods for co-medication

Several HPLC methods were developed to quantify co-medications (levodopa/carbidopa and pramipexole) used in toxicokinetic studies with safinamide in rat, rabbit and monkey (studies 0070/470; 1000-0293; 1004-071197; 1004-071199; 0070/471; and 1004-071198). Precision and accuracy were ≤15%. Storage stability and dilution integrity were shown.

2.3.3.2. Absorption

The bioavailability after oral administration ranged from 33 to 92% in rats and does not seem to depend on the feeding status. The bioavailability was 76 to 95% in monkeys and 95% in humans. Clearance of safinamide was 1.7-2.8 L/h/kg in rat, but much lower in monkey (0.45 L/h/kg) and humans (0.077 L/h/kg). The volume of distribution was larger than the water volume in rat, monkey and human, indicating wide tissue distribution. Gender differences were observed in mice and rat, but not in monkey.

The half-life of safinamide is 1.2-2.1 hours in rat, 5.1-13 hours in monkey and 20-40 hours in humans. Furthermore, a half-life of 2.5 hours for NW 1153 and of 8.5 hours for NW-1689 was observed in rat. In monkey, a half-life of 11.4 hours for NW-1689 and of 10.5 hours for NW-1689 glucuronide was observed. Much longer radioactivity half-lives were observed (>77 hours).

The exposure increases dose proportional in mice (100-375 mg/kg) and in monkey (7.6 to 70 mg/kg). In rat, the increases in Cmax and AUC were more than dose proportional from 5-150 mg/kg, but less than dose proportional at higher dosages. Metabolites NW-1153 and NW 1689 increase more than dose proportional compared to the administered safinamide dose in rat based on one study, but not in another study. Therefore, the results are inconclusive in rats. In monkey, the exposure to NW-1153 and NW 1689 is dose proportional.

After repeated dosing, safinamide accumulation occurred in rat up to 80 mg/kg while no change was observed at a dose of 125 and 200 mg/kg. Accumulation of safinamide was also observed in pregnant rabbits and monkeys. In addition, accumulation of NW-1153 and NW-1689 was observed after repeated dosing with safinamide in rat and monkey, but not for NW-1199.

2.3.3.3. Distribution

Safinamide is moderately to highly bound to plasma proteins in mouse, rat, rabbit, mini-pig, dog, monkey and human, while metabolite NW-1153 is moderately bound and metabolite NW-1689 very highly bound (>99%). The plasma-protein binding is comparable across non-clinical species and humans, and concentration-independent. Safinamide and NW-1153 are more distributed to erythrocytes than to plasma in mouse, whereas they are approximately equally distributed between erythrocytes and plasma in rat, rabbit and dog. In monkey and human, safinamide and NW-1153 are mainly found in plasma. The metabolite NW-1689 is almost exclusively present in plasma in all species.

Drug-related radioactivity is widely distributed to tissues with highest concentrations were observed in the lachrymal gland, spleen, lung, salivary gland, epididymis, brown fat and tissues associated with absorption, metabolism and excretion of safinamide. Passage over the testis-blood barrier was observed. In addition, passage over the blood-brain barrier was observed with brain-to-plasma ratios ranged from 4.5 in Cynomolgus monkeys to 20 in mice. Maximum brain concentrations occurred at 0.5 (mice) to 3 (Cynomolgus monkeys) hours post-dose. Following repeated dosing, free concentrations of safinamide in rat brain corresponded roughly to free concentrations in plasma. Furthermore, reversible melanin binding was observed. Estimated terminal half-lives of total radioactivity are 34-40 hours in liver and lachrymal glands, ~50 hours in plasma, 51-59 hours in kidneys, 70 hours in adrenals, 65 hours in pigmented eyes and 91 hours in pigmented skin. Accumulation in these tissues is therefore possible after repeated once-daily dosing in humans.

In vitro experiments indicate that safinamide is rapidly distributed to hepatocytes via passive diffusion and accumulates there due to lysosomal trapping. Lysosomal trapping is likely to occur in other cell types.

2.3.3.4. Metabolism

Safinamide is extensively metabolised in the non-clinical species and humans. Several enzymes are involved in the biotransformation of safinamide, however not all enzymes involved were identified. The major route of biotransformation of safinamide to NW-1153 is via unspecified amidases. The company has shown that FAAH catalyses the formation of NW-1153 at extremely low rates. Therefore, significant contribution of other amidases to NW-1153 formation is likely and the applicant is requested to identify the major amidases involved in the NW-1153 formation**.**

Thereafter, NW 1153 is further metabolised to Met-A and Met-X via an N-dealkylation by an unknown enzyme, which is followed by biotransformation to NW-1689. Safinamide is to a minor extent metabolised to NW-1199 via CYP enzymes. However, the enzymes involved were not identified. CYP3A4 and to a minor extent CYP2J2 and 2C19 are involved of the direct metabolism of safinamide to Met-A. Met-A is further metabolised by MAO-A to Met-X which is further metabolised to NW-1689 via ALDH2 and to a minor extent via ALDH7A1. NW-1689 is glucuronidated by UGT1A1, 1A3, 1A7, 1A9 and 2B15 to NW-1689 glucuronide. NW 1199 is a minor human metabolite, therefore the Applicant is not warranted to investigate which CYPs are involved in the formation of NW-1199. As NW-1153 plasma levels are relatively low and NW-1153 is not expected to contribute significantly to the toxicity of safinamide, the enzyme(s) further metabolising this intermediate are considered to be of lesser importance and do not have to be elucidated.

Considerable species differences exist in the metabolism of safinamide, with monkey being most comparable to humans. No unique human metabolites are formed. NW-1689 is generally the most important circulating component in plasma of all species.

2.3.3.5. Transporters

Safinamide is not a substrate for P-glycoprotein. Based on preliminary data, safinamide is not a substrate for BCRP after it reaches the systemic circulation. However, it is unknown if safinamide is a substrate for BCRP in the intestine. In addition, safinamide is not a substrate for OATP1B1 and 1B3 after it reaches the systemic circulation, but it could be a substrate in the portal vein. Currently available data indicate that safinamide is not a substrate for OATP1A2 and 2B1, but the applicant was asked to provide the final study report of the in vitro substrate studies with safinamide for BCRP, OATP1B1, OATP1B3, OATP1A2, and OATP2B1 when available.

NW-1153 is only a minor metabolite in plasma, but a major metabolite in urine (approximately 25% of the recovered radioactivity in human urine). Drugs that are inhibitors of OAT3 given concomitantly with safinamide may reduce clearance of NW-1153, i.e., and thus may increase its systemic exposure. The systemic exposure of NW-1153 is low (1/10 of parent safinamide). This potential increase is of no clinical relevance as NW-1153, the first product in the metabolic pathway, is further transformed to secondary and tertiary metabolites. No conclusions can be drawn for the transporters OAT1 and OCT2, since the investigated concentrations were higher than the $C_{max,unbound}$. Final conclusions can be drawn when all data are submitted by the Applicant post-authorization.

2.3.3.6. Excretion

In all non-clinical species except in dog, safinamide is mainly excreted as metabolites via renal excretion (~60-75%). Also in human, the majority of safinamide is excreted via renal excretion (~75%) and faecal excretion is almost absent. Faecal excretion is predominantly due to biliary excretion in rats. The metabolite profiles of the excreta cannot be used for interspecies comparison, as they are incomplete (due to a too short sampling period).

The excretion of safinamide in milk has not been investigated. Mechanistic studies suggested that exposure to safinamide and/or its metabolites through the milk is the most likely cause for the observed neonatal hepatotoxicity. Further studies on excretion in milk are not warranted as the SPC states that safinamide should not be given to lactating women.

2.3.3.7. Pharmacokinetic drug interactions

Safinamide is not a CYP inhibitor at clinically relevant systemic concentrations (25 µM). It is an *in vitro* time dependent inhibitor of CYP1A2, however in a clinical DDI study with caffeine, no clinically relevant DDIs were observed via CYP1A2 inhibition. No clinically relevant CYP inhibition was observed for NW-1153, NW-1689 and NW-1689 glucuronide.

Safinamide and its metabolites are not CYP inducers in the non-clinical species. However, induction via PXR, CAR and AhR is species specific. In contrast, in humans safinamide and its metabolites may be an inducer of CYP3A4 at clinically relevant intestinal (99 µM) and portal vein concentrations (60 µM), but not at maximal systemic concentrations (25 µM). In addition, safinamide may be an inducer of CYP2B6 at clinically relevant portal vein concentrations. In a clinical DDI study, safinamide led to a 20% reduction in midazolam concentrations thus confirming that safinamide is a weak CYP3A4 inducer in humans.

Safinamide and its metabolites NW-1153 and NW-1689 are not inhibitors of extracerebral levodopa decarboxylase, dopa decarboxylase and COMT. Safinamide, NW-1153, NW-1689 and NW-1689 glucuronide are not ALDH inhibitors at clinically relevant systemic concentrations.

Safinamide is an inhibitor of BCRP in the intestine, but not at systemic exposure. NW-1153 is only a minor metabolite in plasma, but a major metabolite in urine (approximately 25% of the recovered radioactivity in human urine). Therefore, information on the inhibition potential towards OCT2, MATE1 and MATE2-K was requested. The requested data were to be generated by an ongoing study (at the time of MAA), and were to be evaluated when the protocols would be presented as part of the recommended post-authorization measures.

NW-1153 appears not to be an inhibitor of OCT2, MATE1 and MATE2-K. However, conclusions can only be drawn when all data are submitted by the Applicant and it is clear how the experiments were performed (*e.g.* positive controls).

Several enzymes are involved in the biotransformation of safinamide (amidases, CYP3A4, MAO-A, ALDHs, UGTs and unidentified enzymes). Since, the extent of the involvement of each enzyme is not fully known, it is unknown if other drugs have a potential to lead to DDIs due to inhibition of enzymes involved in the metabolism of safinamide. In a clinical study, ketoconazole had no clinically relevant effect on safinamide and its metabolites when co-administered (see clinical assessment), indicating that the involvement of CYP3A4 in the biotransformation pathway is minor.

2.3.4. Toxicology

A large number of toxicology studies have been performed, probably reflecting the long period of development of the compound by different companies. Species differences among the non-clinical species and between the non-clinical species and humans are identified. Monkey is the most comparable species to humans for the metabolite profile. Between the rodent species, mice show a more similar metabolite profile to man than rats. In the assessment the focus was laid with those studies considered most relevant.

It should be noted that safinamide contains a nitrogen atom that can be protonated and has a pKA of 7.4. Due to these characteristics it may accumulate in acidic cell compartments (Marceau et al., 2012), as was also suggested by a kinetic study with rat hepatocytes.

CNS

Adverse CNS effects, including tremors, abnormal coordination, clonic contractions and convulsions leading to death were seen at high doses in toxicity studies. Convulsions were encountered in monkeys (≥70 mg/kg/day, 39-wk), rabbits (50 mg/kg/day, embryo-foetal), rats (100 mg/kg/day, carcinogenicity) and mice (≥ 200 mg/kg/day, 4-wk & carcinogenicity). Various CNS signs (tremors, abnormal coordination etc.) were usually prodromal events to convulsions. These convulsions occurred at exposures that were greater than human exposure at 100 mg/day i.e. in monkeys x12.8 (AUC) and x16.8 (Cmax), in rabbits x3.2 (AUC) and x7.7 (Cmax), in rats x1.6 (AUC) and x3.9 (Cmax), and in mice x2.8 (AUC) and x4.9 (Cmax). No mechanistic explanation was provided. Prolonged, high intracellular concentrations of safinamide/metabolites, eventually disrupting normal function could be a possible explanation. However, according to the Applicant, no pattern of treatment related seizures, seizure-like events or adverse CNS events has been reported in over 2000 PD patients, with over 900 subjects receiving safinamide treatment for 1 year or more.

Biochemistry

Reversible changes in some clinical chemistry parameters (i.e., increases in alkaline, phosphatase, ALT, urea, creatinine, cholesterol, triglycerides and decreased glucose, levels) were observed at doses as low as 30 mg/kg/day in rats and 50 mg/kg/day in monkey. At these dose levels, these changes were not associated with target organ toxicity, and may reflect some decrease in normal function of organs involved in metabolic homeostasis (liver, kidney, or endocrine tissues).

Hepatotoxicity

At higher dose levels, liver was a potential target organ in rats and mice but not in monkeys. At 4 weeks in rats, there was fatty change at ≥ 50 mg/kg/day, increased weight at ≥ 60 mg/kg/day, centrilobular hypertrophy and increased serum enzymes at ≥ 200 mg/kg/day. At 13 weeks, there was increased alkaline phosphatase at 80 mg/kg/day, increased liver weight was seen at ≥ 30 mg/kg/day. There were no changes in the 26 week study (high dose, 45 mg/kg/day = NOAEL). In the 13-week pre-carcinogenicity studies, there was hypertrophy (rats and mice ≥ 100 mg/kg/day) and fatty change (mice 375/250 mg/kg/day). In the carcinogenicity studies, there was hypertrophy (rats & mice ≥ 50

mg/kg/day) and vacuolation (mice ≥100 mg/kg/day). In rats, the safety ratios based on exposures at the animal NOAEL (45 mg/kg/day) and at the patient therapeutic dose (100 mg/day) were x1.3.

Again no mechanistic explanation was provided, but chronic exposure and high intracellular concentrations of safinamide or metabolites could be a causative factor for the observed toxicity. Amiodarone, an antiarrhythmic drug with strong lysosomotropic properties is associated with liver toxicity in humans (Schneider et al 1997). According to the Applicant, no systematic changes in liver function tests (LFTs) have been detected in over 2000 PD patients exposed to safinamide, of which 1100 have been treated for >6 months, over 900 have been treated for 1 year or more and 300 subjects treated for 2 years or more.

Immune system

The presence of foamy macrophages was inconsistently noted in rats and with a lower incidence, in monkey studies. In rats minimal to moderate foamy macrophage infiltration was seen in repeat dose toxicity studies at doses of 60 mg/kg/day, while no effects were seen in 13- and 26-week toxicity studies at doses up to 50 mg/kg/day. Generally, foamy macrophages were limited to the lungs, although in a 4-week toxicity study similar cells were seen in the thymus, liver, uterus and vagina. In monkeys, infiltration with foamy macrophages was seen in lymph nodes, thymus and spleen at doses of 80 and 120 mg/kg/day in a 4-week repeat dose toxicity study. No effects were seen in subsequent monkey studies up to 39 weeks of duration at doses up to 70 mg/kg/day. In the second 26-week rat study, EM examinations showed that the alveolar macrophages contained concentric multi-lamellar, myeloid body-like inclusions in the cytoplasm, which were considered indicative of a phospholipidosis condition. Foamy macrophages are a typical finding for lysosomotropic compounds as has been described amongst others for chloroquine and suramin (Schneider et al 1997).

Adrenal gland

Adrenal gland changes were noted in both monkeys and rats. Increased weight and adrenal cortical hypertrophy occurred in different studies in rats at doses ≥50 mg/kg/day. Similar effects were seen in the 4-week monkey studies at doses ≥40 mg/kg/day. In the subsequent sub-chronic and chronic toxicity studies at doses ≥50 mg/kg/day, lipofuscin inclusions were noted in the adrenal cortex of monkeys. Inconsistent results were obtained from the serum cortisol and ACTH level measurements performed in monkeys of two 4-week studies and one 39-week study. There were no clear adrenal cortical changes in mice, besides diffuse hypertrophy of the zona fasiculata in male dosed above MTD. Adrenal changes were shown to be reversible following an adequate withdrawal period. Again, no mechanistic explanation was provided, but the lipofuscin accumulation observed in monkeys suggests the possibility of lysosomal/autophagal dysfunction possibly associated with accumulation of safinamide in the tissue. According to the Applicant, this phenomenon should be seen as a "wear and tear" pigment, which accumulates in the adrenals and other organs over the life of an animal and is considered not toxicologically relevant. Furthermore, there was no evidence of altered adrenal function in clinical studies.

Retina

Thinning and degeneration of the outer retina layer were observed in the rodent repeated-dose toxicity studies and can briefly be summarized as time and dose dependent; occurring in pigmented and albino strains; exacerbated by high light intensity levels; not exacerbated by combination treatment with levodopa/carbidopa but slightly exacerbated by pramipexole combination treatment; not associated with melanin binding or undue sensitivity to UV light; correlating with changes in ERG and SD-OCT; apparent early photoreceptor changes at 24 hours after start of treatment by EM examination; reversible after 3 days of treatment; safinamide is probably the causative toxicant and not the metabolites of safinamide.

The Applicant considered the retinal effects in rodents not relevant for humans, claiming that safinamide-related retinal atrophy occurs only in rodents and not in monkeys, even after long-term administration and even when combined with other drugs associated with retinal degeneration in rats and claiming that there was no increased risk of retinal degeneration in patients treated with safinamide.

Generally safety margins if existent were low, especially for the retinal toxicity observed in rats, but in monkeys safety margins (6.6-9.5 based on AUC) were more acceptable.

Genotoxicity, carcinogenicity

A battery of genotoxicity assays were performed to assess the genotoxic potential of Safinamide, metabolites NW 1153, NW 1689 and NW 1689-AG, the acyl glucuronide form. Safinamide and its metabolites have shown no genotoxic potential.

In two long term carcinogenicity tests in mice and rat, safinamide did not show tumorigenic potential.

Fertility and pregnancy

In rat male and female fertility studies no effects on fertility parameters were observed up to at least 3.8 and 3-fold the anticipated maximal clinical exposure. However, at exposures above 1.4-fold the human clinical exposure, sperm abnormalities were observed. Considering the low safety margin and the differences between sperm levels in rat and in man, an effect on male fertility cannot be excluded.

In embryo-fetal developmental studies in rats and rabbits malformations were induced at safinamide exposures 2 and 3-fold above human clinical exposure, respectively. In the rat study no NOAEL was established and at the lowest dose level slightly enlarged ureter(s), globular heart, oedema of hindlimbs and displaced testes were observed. In rabbits, malrotated limbs were observed. Although the incidence of these malformations was low, due to the low or absent safety margins, safinamide must be considered to be potentially teratogenic.

In a pre- and postnatal developmental rat study, mortality, absence of milk in the stomach and neonatal hepatotoxicity was observed at dose levels similar to the anticipated clinical exposure. Mechanistic studies showed that pre-natal exposure and exposure through the milk induced the hepatotoxic effects in the pups. Women treated with safinamide should not breastfeed their children.

Local tolerability

Acute dermal and eye irritation studies in rabbits revealed that safinamide is not irritant to the skin while it is severely irritating to the eye.

Dependence and abuse potential

Dependence potential was addressed by the Applicant in response to the D120 LoQ. A behavioural study in rhesus monkeys showed that safinamide could enhance the discriminative stimulus of cocaine, which is explained by the Applicant as a consequence of its pharmacological activity of enhancing the dopaminergic transmission. It is concluded that there is little evidence to suggest that safinamide would pose a problem as regards abuse potential in PD patients. With respect to a potential interaction with DA releasing agents, there remains some uncertainty. It can be accepted that no further studies are performed at this stage.

2.3.5. Ecotoxicity/environmental risk assessment

Table 3 Summary of main study results

Substance (INN/Invented Name): Safinamide					
CAS-number (if available): 202825-46-5					
PBT screening		Result			**Conclusion**
Bioaccumulation potential – log *K*ow	OECD 107 OECD 117	Log D_{ow} = 2.2 (pH 7.4) Log D_{ow} = 2.4			not potential B
PBT-assessment					
Parameter	**Result relevant for conclusion**				**Conclusion**
Bioaccumulation	log *K*ow	Log D_{ow} = 2.2 (pH 7.4) Log D_{ow} = 2.4			not B
	BCF	study not triggered			
Persistence	ready biodegradability	not readily biodegradable			not P
	DT50	Highest DT_{50} = 16.3 d (details below)			
Toxicity	NOEC	0.19 mg/L			not T
	CMR	No harmonized classification			
PBT-statement :	Safinamide is considered not to be PBT, nor vPvB				
Phase I					
Calculation	**Value**	**Unit**			**Conclusion**
$PEC_{surface\ water}$, default F_{pen}	0.5	µg/L			> 0.01 threshold
Other concerns (e.g. chemical class)	not investigated				
Phase II Physical-chemical properties and fate					
Study type	**Test protocol**	**Results**			**Remarks**
Adsorption-Desorption	OECD 106	PM			in progress
Ready Biodegradability Test	OECD 301	not readily biodegradable			0% degradation after 28 days
Aerobic and Anaerobic Transformation in Aquatic Sediment systems	OECD 308	$DT_{50.\ water}$ = 1.7 and 2.3 d at 20 °C $DT_{50.\ sediment}$ = 10.4 and 16.3 d at 20 °C $DT_{50,\ total\ system}$ = 1.8 and 3.5 d at 20 °C % shifting to sediment = 10.1 (day 8) and 12.3% (day 2)			Significant shifting to sediment observed.
Phase IIa Effect studies					
Study type	**Test protocol**	**Endpoint**	**value**	**Unit**	**Remarks**
Algae, Growth Inhibition Test / *Desmodesmus subspicatus*	OECD 201	NOEC EC10	0.19 2.8	mg/L	growth rate
Daphnia magna acute toxicity	OECD 202	EC50	23	mg/L	immobility
Daphnia sp. Reproduction Test	OECD 211	NOEC EC10	0.29 0.84	mg/L	reproduction
Fish, Early Life Stage Toxicity Test/ *Danio rerio*	OECD 210	NOEC	3.4	mg/L	survival
Activated Sludge, Respiration Inhibition Test	OECD 209	EC10	85	mg/L	respiration
Phase IIb Studies					
Sediment dwelling organism / *Chironomus riparius*	OECD 218	NOEC	PM	mg/kg	in progress

The risk assessment can be concluded for the STP and the surface water and groundwater compartment. No risk is anticipated for these compartments.

Safinamide is considered not PBT, nor vPvB.

However, the dossier was considered incomplete.

A study determining the adsorption constant of the active has not been submitted. QSAR values were not accepted. The applicant was requested to complete the dossier and to submit an adsorption-desorption study using a Batch Equilibrium Method (OECD 106) 2 types of sewage sludge.
The applicant was also recommended to determine the organic carbon content of the sludges. This study was ongoing at the time of the assessment.

In case Koc sludge >10,000 L/kg, a soil risk assessment is triggered (see EMEA/CHMP/SWP/4447/00 corr 1).

The water/sediment simulation study suggests that more than 10% of the compound shifted to sediment at or after 14 days. Therefore, a sediment risk assessment is triggered. The applicant committed to perform a study on sediment dwelling organisms to evaluate the potential risk to sediment organisms, but requested to conduct a study according to OECD 218 instead of OECD 219. This was recommended by the CHMP.

As a sediment risk assessment is triggered, the applicant was recommended by the Committee to conduct an adsorption-desorption study using a Batch Equilibrium Method (OECD 106) using 3 soil types to enable calculation of $PEC_{sediment}$.

To assist the persistence of a compound in the environment it is necessary to normalize the DT50 to an environmentally relevant outdoor temperature, which is agreed to be 12°C in the EU. The applicant was recommended to do so in the revised ERA.

The DT_{50} values for safinamide and its metabolites, Met 1, Met 2 and Met 3 were recalculated from the data obtained at 20 ± 2°C in two aquatic sediment systems using the Arrhenius equation to DT_{50} values at 12°C, which will be added to the revised ERA. From these DT_{50} values it does not appear that safinamide or its metabolites, Met 1, Met 2 and Met 3**,** meet the persistence criterion in sediment or whole-system (DT_{50} < 120 days).All the above mentioned issues can be addressed with post-authorization measures as recommended by the CHMP.

2.4. Discussion on non-clinical aspects

The reversible inhibition of MAO-B occurs at relatively low concentrations and also can be measured *ex vivo* after modest doses of safinamide in animals. Reducing dopamine catabolism by MAO-B inhibition is an established mode of action which substantiates the modest increase in ON-time in MPTP-lesioned cynomolgus or rhesus monkeys when these animals are treated with L-DOPA. Taken together these non-clinical data support and explain the increase in ON-time observed in PD patients treated with safinamide as add-on therapy next to L-DOPA. However, efficacy or mode of action of safinamide for use as add-on therapy in PD patients next to a dopamine agonist has not been investigated non-clinically.

Multiple modes of action next to safinamide's action as a MAO-B inhibitor have been theorized, notably sodium channel inhibition, calcium channel inhibition, reduction of excessive glutamate release, and inhibition of dopamine and serotonine transporters. It is uncertain whether the brain concentrations in patients receiving a maximal daily dose of safinamide of 100 mg would be sufficient for these additional mechanisms to be demonstrated as meaningful in the therapeutic effect.

Although the Applicant tried to argue by providing a justification based on PK/PD estimation of the pharmacodynamically available safinamide brain concentrations in humans and their possible correlation to *in vitro* concentrations and brain concentrations in animals at which relevant effects on sodium glutamate release were measured, from the assessment it was concluded that at therapeutic concentrations in humans inhibition of brain MAO-B was the most likely mechanism responsible for the increase in ON time in PD patients simultaneously treated with L-DOPA. For all other claimed mechanisms

of safinamide the evidence provided was not considered convincing enough for the CHMP to conclude that these were relevant for PD patients treated with safinamide.

A modest increase of ON-time could be demonstrated in MPTP-lesioned cynomolgus and rhesus monkeys. However, a reduction in dyskinetic score observed in the cynomolgus monkey was not replicated in an independent experiment in rhesus monkeys. Therefore the claim from the Applicant that safinamide can reduce dyskinesia associated with dopaminergic treatments in PD patients was considered by the Committee as not sufficiently supported by the non-clinical data.

Outcome parameters assessed in cardiovascular safety pharmacology studies were only minimally affected and/or showed only changes at high safinamide doses or concentrations. These results indicated that safinamide did not pose an increased cardiovascular risk.

Although initial binding assays suggested a potential interaction of safinamide and/or its metabolites with imidazoline receptor type 2, sigma receptors type 1 and 2, muscarinic receptor type 3 at clinically relevant concentrations, follow-up studies did not reveal agonist activity of safinamide and/or its metabolites and showed antagonist activity only at concentrations, which are not considered clinically relevant. The functional data can be considered to overrule the initial binding data. Consequently, a clinically relevant interaction with M3-antagonists in patients is not expected. Pharmacokinetically, the main issue is a lack of information on the identity of the amidases involved in the major routes of metabolism of safinamide, which is to be resolved by the respective measure introduced in the RMP i.e. a study to investigate in vitro which amidase enzymes are involved in its biotransformation to NW-1153.

Furthermore information on transporters, with potentially relevant for drug-drug interactions is very limited, but this will also be addressed by the CHMP recommendation to submit the reports of in vitro studies evaluating whether safinamide affects the function of several transporters.

The CHMP considered that the questions about amidase enzymes' involvement in the biotransformation of Safinamide to NW-1153, and the ones with regard to clinical DDI study with a BCRP substrate with a Tmax ≤2 hours, needed to be addressed in specific measures included in the RMP, and linked to the relevant missing information. The Committee also recommended that the data from the studies on ERA (please see section

Ecotoxicity/environmental risk assessment) are provided post-approval.

Discussion on retinal degeneration

Based on the non-clinical data only, it could not be concluded whether the observed retinal toxicity was rodent specific. It was clear that rats show a greater sensitivity as retinal toxicity was consistently observed in them, whereas in monkeys only slight effects on mitochondria in photoreceptor cells were seen. In only one monkey at a mid-dose level of 10 mg/kg/day safinamide plus 2 mg/kg/day pramipexole, more extensive unilateral retinopathy was seen and this was interpreted as a spontaneous lesion by the applicant. The applicant tried to argue that these observations in monkeys were not to be considered toxicologically relevant, but for the CHMP they did introduce another level of uncertainty about the rodent-specificity of the retinal changes. Furthermore, conclusions on any findings in monkeys (or the lack of them) should be taken with caution because more detailed histological observations (counting of rows of nuclei in the outer nuclear layer) was only done in a few studies with 91 animals, and a more detailed electron microscopic investigation was only done in a single monkey study.

The studies in rats provided a more elaborate and detailed structural and temporal description of the retinopathy, but a mechanistic explanation was lacking. This made it difficult to assess the relevance of the retinal lesions to any potential similar effects on humans in the setting of the intended clinical use. In an attempt to clarify mechanistically the observations, the lysosomotropic properties of safinamide were considered by the Applicant and the results demonstrated that the mechanism was not similar to chloroquine, a known lysosomotropic retinal toxicant. Yet high concentrations in other acidic compartments, e.g. in mitochondria, were not further investigated. Hypothetically, impaired lysosomal/autophagal function of retinal pigment epithelium (RPE) cells may have deleterious effects on the photoreceptor cells (PRC) as has been proposed for chloroquine and other retinotoxic substances (see Audo & Warchol 2012, and references mentioned in this review). Additional experimental data submitted provided some evidence that phagocytosis by and cytotoxicity of RPE cells was not affected at clinically relevant concentrations of safinamide, although uncertainties on extrapolation of *in vitro* to *in vivo* data and vice versa remained. Also interference of safinamide with degradative processes within the RPE and subsequent potential accumulation of photoreceptor outer segment remnants and degradants had not been investigated. Therefore, although a direct effect on phagocytosis or acute cytotoxic effect on RPE cells seemed unlikely, potential interference with other elements relevant for the degradation and recycling of outer segment remnants by RPE could not be fully excluded on the basis of the experimental results provided.

Another hypothesis explaining the findings could be that excess dopamine diffusing from amacrine cells, due to reduced re-uptake and/or reduced metabolism could be a contributory factor leading to oxidative stress (Toler 2012). The study investigating dopamine metabolism in rat retinas was considered inconclusive in this respect as dopamine and dopamine metabolite levels in the retinas were assessed only one hour after the administration of safinamide.

Although retinal toxicity was present in rats, and its mechanism had not been elucidated, the lack of consistent similar findings in humans diminished the concern for potential similar effect on the patients. Nevertheless, based on the non-clinical evidence available, the CHMP was of the view that retinal degeneration should be considered as an important potential risk and followed up on through the proposed routine and additional pharmacovigilance activities, as described in the RMP.

2.5. Conclusion on the non-clinical aspects

Safinamide is a reversible MAO-B inhibitor. Non-clinical data support a modest increase in ON-time when administered in combination with L-dopa/carbidopa.

From a non-clinical point of view it was considered that Xadago could be granted a Marketing Authorisation. With regards to the environmental risk assessment, the CHMP concluded that the dossier was not complete and recommended that several elements be investigated post-authorisation, as detailed in section 2.3.5.

2.6. Clinical aspects

2.6.1. Introduction

Safinamide is an α-aminoamide derivative. It was claimed to act through a multi-modal mechanism of action:

- reversible and selective Monoamine Oxidase B (MAO-B) inhibitor, which is more than 1000-fold selective over MAO-A. Inhibition of the MAO-B pathway is thought to prevent the breakdown of both endogenous and exogenous dopamine in the brain.

-reduction of stimulated glutamate release in the basal ganglia, without affecting basal glutamate levels.

-controlling the neuronal excitability by blocking voltage-gated sodium (Na^+) channels in a state-dependent manner. Safinamide also modulates calcium (Ca^{++}) channels.

At higher dosages, safinamide binds to monoamine transporters DAT, SERT, NET, which are responsible for the reuptake of their associated amine neurotransmitters serotonin, dopamine, and norepinephrine, respectively.

The first in man Phase I study for safinamide was conducted in September 1999. Safinamide was initially explored in subjects with epilepsy. Safinamide has also been explored in cognitive dysfunction, but there was no intention to continue clinical development for either epilepsy or cognition at the time of this application.

Because of its MAO-B inhibitory properties, an exploratory Phase II randomised placebo-controlled study in subjects with early PD was performed in 2001, indicating an dose-dependent improvement of motor symptoms in a sub-group of patients using dopamine-agonist at baseline (study 009). Later, also studies were performed in advanced PD patients with motor fluctuations, with safinamide as add-on to levodopa therapy.

The Phase III program consisted of two 24-week placebo-controlled studies add-on to a single DA-agonist in early-stage PD subjects (non-fluctuators), and two 24-week, placebo-controlled studies in mid- to late-stage fluctuating PD subjects on L-dopa and other concomitant anti-Parkinson's medications. Subjects completing the 24-week trials could continue treatment in long-term (up to 18 months), double-blind, placebo-controlled extension studies, and/or enter an open-label study in which all subjects received safinamide.

Safinamide was originally developed by Newron, but in 2006 Merck Serono acquired the rights. Merck-Serono interrupted the continuation of a prescheduled double-blind extension phase of a Phase III trial in early PD (MOTION Study) , as in the first placebo-controlled phase of 24 weeks the primary endpoint was not met. In 2012, Newron regained full global rights to safinamide from Merck-Serono. In April 2012 the Zambon Group gained rights to commercialise safinamide globally, excluding Japan and other key Asian territories, where Meiji Seika has the rights to develop and commercialise.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

A request for GCP routine inspection was adopted by the CHMP for the clinical Study 27918 (MOTION trial). The inspection was performed and it was concluded that the study report could be used for evaluation and assessment of the application.

2.6.2. Pharmacokinetics

ADME (absorption, distribution, metabolism, excretion)

The absolute bioavailability of safinamide is high (mean 95%) after administration of 50 mg as tablets under fasting conditions. As the solubility is low (as described in the quality section) safinamide can be classified according the BCS as a Class II drug. Safinamide is not subjected to a significant first pass effect.

After intravenous administration the estimated clearance is about 4.6 L/h and the volume of distribution 174 L. The elimination half-life is about 26 hours.

After administration of a single oral dose of safinamide 100 mg the maximum plasma concentration was found after approximately 2 hours, the C_{max} was approximately 650 ng/mL and the AUC 19000 ng/mL×h.

In several studies a secondary peak was observed. The second peak was seen about 45 minutes after the first peak. The secondary peaks are most probably due to the disposition of safinamide and although the most obvious explanation would suggest this may be due to intestinal re-absorption after biliary elimination; i.e. associated with entero-hepatic cycling (EHC), data from the peaks observed after i.v. dosing contradict this supposition (Roberts M et al. 2002).

Two food effect studies were conducted. In the first study (N=14) no food effect was found and in the second study (N=6) the C_{max} was slightly lower (16%) after intake with food; in both studies the T_{max} was delayed. Based on these studies it could be concluded that food does not have a significant influence on the bioavailability of safinamide.

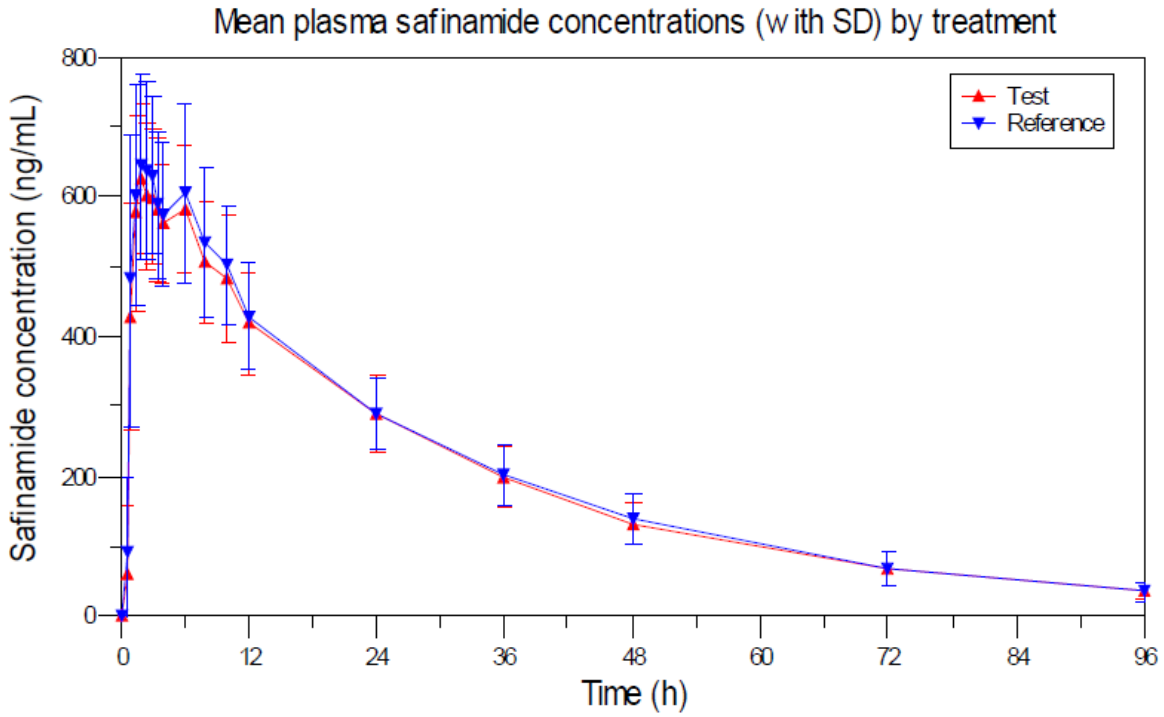
The volume of distribution at steady state (V_{ss}) is 165 L (V_z is 174 L indicating that safinamide is well distributed. This is in line with safinamide's lipophilicity and high permeability.

The extent of protein binding in human plasma was concentration independent, the unbound fraction was 11-12% for safinamide, and for the metabolites 25-29% for NW-1153, <.0.2% for NW-1689 and 2.6% for the acyl glucuronide of NW-1689 (NW-1689 AG).

The total clearance was determined to be 4.6 l/h classifying safinamide as a low clearance drug. The mean elimination half-life was 26 hours with a range of 20-40 h, allowing for once a day administration. In the mass balance study, approximately 78% of the radioactivity was recovered within 192 h (76% in urine and 1.5% in feces); the recovery is consistent with the radioactivity elimination half-life of ~80 h (CRO-02-33). The excretion data and metabolic pattern confirmed that safinamide is extensively metabolized, only 5-7% of the administered dose was found unchanged in urine within 48-72 h and increased only slightly afterwards.

A typical plasma-concentration-time curve is given below (Figure 2).

Figure 2 Mean (SD) plasma concentration-time curves of safinamide after oral administration of 100 mg as two different tablet formulations. (Study EMR701165_021)



test: RC yellow tablets (commercial formulation)

reference: DC tablets (clinical trial formulation)

The metabolic pattern found in several studies submitted was in line with those found in animal studies. Safinamide is extensively metabolised in the non-clinical species and humans. The major route of safinamide biotransformation is via NW-1153 to Met A/Met-X to NW-1689. Safinamide is metabolised to NW-1153 via amidases, however the specific amidase involved had not been identified. The company had shown that FAAH was not the main amidase responsible for the biotransformation of safinamide, but had not evaluated the contribution of other amidases.

Thereafter, NW-1153 is further metabolised to Met-A and Met-X via an N-dealkylation by an unknown enzyme. Safinamide is to a minor extent metabolised to NW-1199 via CYP enzymes. However, the enzymes involved were not identified. CYP3A4 and to a minor extent CYP2J2 and 2C19 are involved in the direct metabolism of safinamide to Met-A. Met-A is further metabolised by MAO-A to Met-X which is further metabolised to NW-1689 via ALDH2 and to a minor extent via ALDH7A1. NW-1689 is glucuronidated by UGT1A1, 1A3, 1A7, 1A9 and 2B15 to NW-1689 glucuronide.

All relevant metabolites (NW-1153, NW-1189, and NW-1689 glucuronide) are considered inactive in terms of efficacy and safety.

The main compound in plasma, exceeding the exposure of the parent drug is the metabolite NW-1689. The other two main metabolites NW-1689 glucuronide and NW-1153 present a smaller fraction accounting to about 20% and 10% of the parent drug exposure total radioactivity in plasma, respectively (Studies 28778, 28559, EMR 701165-21). NW-1153 is a minor metabolite in plasma and is actively excreted via OAT3 to the urine. The exposure to the metabolites of safinamide does not accumulate after repeated administration. In line with this, the metabolic ratio remains unchanged after steady state, compared to single dose administration. The half-lives of the metabolites are comparable to that of safinamide, i.e. 19.5 h, 25.3 h and 26.5 h for NW-1153, NW-1689 and NW-1689 glucuronide, respectively.

In urine, the main metabolites were NW-1153 (14-22% of dose) and NW-1689 glucuronide (11-20% of dose), NW-1689 was detected only in trace amounts. In addition, a few minor metabolites (O-debenzylated safinamide (NW-1199), glycine-conjugated NW-1689 and traces of monohydroxylated safinamide derivatives were found in urine.

Safinamide is a chiral compound, however, inter conversion of S-safinamide to R-safinamide is unlikely to occur *in vivo* as R-safinamide could not be detected (study CRO-02-33).

The pharmacokinetics of safinamide were investigated over a wide range of doses (from 1.5 mg to 700 mg) in different studies. The inter- and intra-individual variability in the pharmacokinetics of safinamide was 15-30% for the C_{max} and AUC's. The mean safinamide concentrations found in patients were comparable with those found in healthy subjects.

PK in special populations

The effect of renal impairment on safinamide pharmacokinetics was investigated in an open-label, parallel-group, single centre, single oral dose (50 mg) study in 24 male and female subjects. Overall, increased exposure of safinamide metabolites was in accordance with available information on their elimination. According to the available data it was agreed by the CHMP that dose adjustment is not needed in patients with mild, moderate or severe renal impairment.

The effect of hepatic impairment was investigated in an open-label, parallel group, single center, single oral dose study. The plasma pharmacokinetics of safinamide are comparable between healthy and Child-Pugh A subjects. An increase in AUC_{0-t} and a longer half-life was observed in Child-Pugh B subjects which points to differences in the elimination between subjects with different hepatic functions. In the SmPC a dose recommendation is given for these patients. No data are available in patients with severe hepatic impairment, and that is why they are contra-indicated according to the SmPC.

No formal studies were conducted on the intrinsic factors gender, age, weight and race. In the population pharmacokinetic analysis of the safinamide data of the Phase III clinical studies no clinical significant effect of gender, age, weight and race was found.

Age was tested as a covariate in the population PK model and was found not to affect safinamide pharmacokinetics significantly.

The population analysis included the data of 209 elderly subjects see Table 4 below:

Table 4 Elderly in POPPK Studies NW-1015/015/III/2003 and NW-1015/016//III/2006

	Age category		
Frequency (N)	65 to 74 yr	75 to 84 yr	⩾85 yr
Total=209	174	35	0

The Applicant did not investigate the effect of gender on the pharmacokinetics of safinamide in a separate study or performed a subgroup analysis with the results of the studies in which subjects of either gender were used. However, the PopPk analysis did not show any effect of gender.

No information of the effect of race on the pharmacokinetics of safinamide was submitted by the company.

In the pop PK study body weight was included as a covariate, in subjects over 100 kg the plasma levels were lower than in subjects with a weight of 70 kg.

Interactions

In vitro
The potential effect on COMT or dopa- decarboxylase, which is involved in the metabolism of L-dopa, and the ALDH inhibition potential of safinamide were investigated. No interactions were observed at clinically relevant systemic concentrations.

The inhibitory potential of safinamide and its metabolites on the transporters P-glycoprotein, BCRP, BSEP, OATP1B1, OATP1B3, OAT1 and OAT4 was assessed. Based on the in vitro studies and Gastro-Intestinal Transit Time simulations, it was excluded that safinamide is an inhibitor of BCRP in the small intestine and could potentially lead to DDIs. The CHMP recommended the conduct of a clinical DDI study with a BCRP substrate with a *Tmax ≤ 2 hours (e.g. pitavastatin, pravastatin, ciprofloxacin, methotrexate, topotecan, diclofenac or glyburide*) to evaluate this potential. Safinamide and its major metabolite, NW-1689, had no inhibitory potential for the other transporters. Based on available data, safinamide did not appear to be an inhibitor of OATP1A2 and 2B1, and NW-1153 was not an inhibitor of OCT2, MATE1 and MATE2-K.

In vivo

Cyp-3A4 inhibitors: From the data available it was shown that the PK of safinamide and its metabolites is not altered when co-administered with the strong CYP3A4 inhibitor, ketoconazole. Small non-clinically relevant changes of the plasma concentrations of safinamide and metabolites were observed.

Enzyme inducers: In study NW-1015/010/II/2002 the interaction with antiepileptic drugs was evaluated. In this study the plasma safinamide levels were about 30% lower in patients using enzyme inducing antiepileptic drugs when compared with those not using enzyme inducers. The data from study NW-1015/010/II/2002 did not support a reliable conclusion of the magnitude of effect of enzyme-inducing drugs on safinamide pharmacokinetics. However, given the range of concentrations observed in these patients, particularly on day 4 where a full concentration-time profile was characterised, and given the potent enzyme inducing drugs that were co-administered, the CHMP agreed that there was good evidence that there will not be a large impact of strong inducers on safinamide plasma concentrations. Therefore, it was considered acceptable not to conduct a specific study with co-administration of a strong enzyme inducer.

CYP1A2 substrate: Concomitant administration of safinamide and the CYP1A2 substrate caffeine resulted in an increased plasma exposure of caffeine. It could be concluded that safinamide is a weak CYP1A2 inhibitor at the dose of 100 mg. This is in line with the results of the *in vitro* studies although the time dependent effect was not confirmed.

CYP3A4 substrate: Safinamide is a weak inducer of CYP3A4, it decreased midazolam exposure by 20%, this effect was considered small and not of clinical relevance. These results were also in line with the results of the *in vitro* studies.

L-Dopa: The results of interaction studies with L-dopa and safinamide in healthy volunteers and Parkinson patients show that safinamide did not affect the PK of L-dopa to a clinically relevant extent. Based on known safety profile and PK variability of levodopa, the acceptance boundaries for L-dopa were predefined at 0.75-1.33, which was considered acceptable. This was line with the results of the preclinical studies in which was also shown that safinamide did not affect the PK of L-dopa. The effect of L-dopa on the pharmacokinetics of safinamide has not been evaluated and was not required as the population PK data in Parkinson patients treated with L-dopa were in line with the safinamide PK data of healthy volunteers.

Other medication used for Parkinson's disease: No pharmacokinetic interaction study with dopamine agonists was performed. The clinical safety of combined use with dopamine agonists was

investigated. Based on the presented PD interaction evaluation it appeared that the risk of neuropsychiatric adverse events seemed to be higher in subjects taking dopamine agonists. This adverse event could be explained by the pharmacodynamic properties of both therapeutic agents. Safinamide is also expected to be co-administered with amantadine and parasympathicolytic Parkinson medication. No pharmacokinetic interaction studies were performed with this concomitant medication, although this medication was also evaluated in the PD interaction study. For amantadine worsening of PD including hallucinations was observed, for the parasympathicolytic Parkinson medication no safety issues were detected. Because pharmacokinetic interactions with dopamine agonists are not expected based on the pharmacokinetic properties of both agents the lack of a PK interaction study was considered acceptable.

Proton pump inhibitors: As the solubility of safinamide is pH dependent a DDI study with a proton pump inhibitor was requested to be presented. As a response, the applicant performed a popPK analysis. The simulations predicted only a slight increase in safinamide C_{max} and AUC of 4 and 10%, respectively, when co-administered with different PPIs. This effect was considered clinically irrelevant by the Committee.

Antidepressants: As serious adverse events have been reported with the concomitant use of other MAO- B inhibitors and antidepressants it was agreed that concomitant use should not be recommended. Additional interaction studies were not required.

Other co-medication: In clinical practice, it can be expected that safinamide will be used in an elderly population. Concomitant use of other medication is to be expected. The potential for pharmacodynamic interactions was evaluated in patients with early and late stage Parkinson's disease, in a safety study. The Breslow-Day test was used to assess AEs in patients on specific concomitant medication. This test can be used to get a first impression of the safety of the combined use of medication, however it cannot be used to show that there are no drug interactions. Based on the results of the PD interaction study, it appeared that concomitant administration of XADAGO™ together with a broad category of commonly used drugs in this patient population (antihypertensive medications, beta-blockers cholesterol lowering drugs, non-steroidal anti-inflammatory drugs, etc.) was not associated with any increased risk for adverse events, however no definite conclusions on the lack of interaction could be drawn. Due to the low potential for interaction of safinamide via CYP and P-gp no additional pharmacokinetic studies with these drugs were considered required by the Committee.

Distribution/Excretion

As safinamide is not a substrate for P-gp and was found to be distributed into the brain tissue in animals, distribution into the human brain was also expected to occur. The *in vitro* substrate studies with safinamide for OATP1B1, OATP1B3, OATP1A2, and OATP2B1 were ongoing at the time of MAA (only preliminary results were provided), and it was recommended by the CHMP to provide the full data when they become available post-approval. The available data indicated that it was unlikely that Safinamide was a substrate for BCRP, OATP1B1, 1B3, 1A2 and 2B1 after it reaches the systemic circulation. This indicated that the transporters OATP1A2 and 2B1 are most likely not involved in the active transport over the blood-brain barrier. NW-1153 is actively excreted in urine (most likely via OAT3).

Elimination

The total recovery found in the mass-balance study was moderate. It was not clear what the fate of the 23% of the administered dose remaining undetected was. The applicant clarified that samples collection beyond 200 h resulted in only 80-90% in animal species and that similar pattern was to be expected in humans. That scenario was considered an acceptable explanation for the expected pattern in humans considering the long elimination half-life of 80 hours.

Metabolism

Safinamide is extensively metabolised. Several enzymes are involved in the biotransformation of safinamide, however not all the involved enzymes were identified during the development programme. Although amidases appear to be the main metabolic enzymes responsible for the biotransformation of safinamide to NW 1153, the specific amidase involved had not been identified. Because metabolism of safinamide through NW-1153 is the main elimination pathway, and since in the future relevant inhibitors or inducers of amidases may become known, it was considered important the amidases involved in this process should be identified and this led to a recommendation from the Committee.

Several other enzymes involved in the metabolism of safinamide were also not identified, however this was not considered a problem as these enzymes were involved in the minor routes of elimination.

This might explain why safinamide metabolism was minimally (approx. 10%) inhibited by the CYP3A4 inhibitor ketoconazole *in vivo*.

At the time of this opinion there were no marketed drugs known to cause clinically significant drug-drug interactions through inhibition or induction of amidase enzymes.

Dose proportionality and time dependent pharmacokinetics

The half-life of safinamide after single and multiple doses was 23.4 h (EMR701165-021) and 23.8 h (IPAS-NW/LD-231-00), respectively. The corresponding AUCs0-∞ after single and multiple oral doses were 19245 ng/ml/*h (EMR701165-021), and 19811 ng/ml/*h (Study 28559), respectively. Using a dosing interval of 24 hours (once daily), steady state is reached after 5 days. The data in humans indicate consistency in the time to steady state based on the reported half-life.

After repeated dosing the pharmacokinetics of safinamide seem not to change in a significant way and the pharmacokinetics seem to be time-independent. The applicant did not provide a formal steady-state study in which the C_{trough} values were measured over several days in steady state. However, in the Clinical Phase III studies 015 and 017, plasma concentrations were measured over a long period of time. From these data it was clear that the pharmacokinetics of safinamide could be considered as time independent.

Pharmacokinetics in Patients

In healthy subjects after administration of 100 mg/day a C_{max} was found of 1200 ng/mL and in patients after administration of 50-100 mg (most patients received 100 mg) a mean concentration of approx. 1000 ng/mL was found in the clinical study 015. However in the other clinical study 016 higher concentrations were found with a difference of 30% to the results from study 015. Even though no explanation (e.g. use of different analytical techniques, salt content versus free base, differences in administered dose and sampling time) was provided, the observed 30% difference in safinamide plasma concentration was not considered relevant for the comparison between patient and healthy volunteer data, as the uncertainty in the plasma concentrations of both studies was similarly high. Despite of this difference between clinical study 015 and 016 it could be concluded that overall the pharmacokinetics in Parkinson patients did not differ significantly from those in healthy volunteers.

Special Populations

Renal Impairment

In subjects with renal impairment, the excretion in urine of safinamide was similar to that in subjects with normal renal function: 3.3% (moderate) and 4.9% (severe). Cumulative recovery of the metabolites was lower in subjects with renal impairment: 26.7% and 22.9% of the dose in subjects with moderate and severe impairment, respectively. In conclusion, safinamide dose adjustment was not considered needed in patients with mild, moderate or severe renal impairment.

Hepatic Impairment
An increase in AUC_{0-t} and a longer half-life was observed in Child-Pugh B subjects which points to differences in the elimination between subjects with different hepatic functions.

The formation of the metabolite NW-1689 was reduced in subjects with hepatic impairment as indicated by a decrease in C_{max}. Terminal $t_{1/2}$ was prolonged by approximately 20 h in Child-Pugh B subjects compared to controls demonstrating that the elimination of this metabolite was also affected. Overall, the net effect on AUC_{0-inf} and AUC_{0-t} is marginal as shown by comparable values across the three groups.

2.6.3. Pharmacodynamics

Based on pre-clinical data, safinamide was speculated to act through multimodal mechanisms of action, including Monoamine Oxidase B inhibition, reduction of stimulated release of glutamate without affecting basal glutamate levels, and reduction of the neuronal excitability by blocking voltage-gated sodium channels and at higher concentrations it inhibition of calcium channels.

The MAO-B inhibitory effect of safinamide was evaluated in healthy volunteers and patients in several studies. In these studies, inhibition of the deamination of C14 –PEA in platelets by the study drugs was measured, as biomarker of central MAO-B activity. The outcomes are summarized in the Table 5 below:

Table 5 Phase I/II studies on MAO-B inhibition.

Study	**Safinamide dose level (number of subjects)**	**% MAO-B inhibition**	**conclusion**
IPAS-NW/ID-231-00 Healthy volunteers (n-=5)	25 µg/kg, single dose 50 µg/kg, single dose 75 µg/kg, single dose 150 µg/kg, single dose	18% 38% 66% 75%	At single dose of approximately 10 mg, an inhibition of 75% was achieved.
IPAS-NW/PAR-254-00 Healthy volunteers (n-=6)	300 µg/kg, single dose 600 µg/kg, single dose	84% 92%	At single dose of approximately 20-40 mg, a near optimal inhibition was achieved.
IPAS-PNU-194-99 Healthy volunteers (n-=8)	2.5 mg/kg single dose 5 mg/kg single dose 10 mg/kg single dose	Complete at all dose levels	This study was not sensitive to establish dose-response relationship.
Study 012 Parkinson Disease Patients (n= 10)	100 mg/day 150 mg/day 200 mg/day Multiple dosing	Complete at all dose levels	This study was not sensitive to establish dose-response relationship.

Based on these data, it was concluded that safinamide at doses over 40 mg, induced a complete blockade of MAO-B activity in platelets, which is a biomarker for central MAO-B activity.

In first-in-men study IPAS-PNU-194-99 in healthy volunteers, doses of 10 mg/kg did not affect MHPG (3-Methoxy-4-hydroxyphenylglycol) levels in plasma, a biomarker of MAO-A inhibition, compared to placebo. Three Phase I trials in healthy volunteers did not reveal a change in blood pressure at tyramine challenge, in contrast to the positive control phenelzine. Base on this it could be concluded that at therapeutic doses, safinamide has limited impact on MAO-A activity, and therefore no significant interaction with tyramine in food is expected.

Safinamide was also explored in epilepsy where in a short-term uncontrolled study a reduction of seizures compared to baseline was observed (an effect which was theorized to result from the activity of safinamide on sodium channels). However, it was difficult to draw conclusions from this study because of its open-label design.

PK_PD analysis

The relationship between ON-time and safinamide plasma levels was evaluated in a PK-PD model. The clinical data for this model were derived from Study 016. No clear correlation between plasma levels and efficacy outcome was found.

Potential pharmacodynamics interactions

The risk of safinamide in combination with specific drugs of interest was explored in the pooled safety dataset of the main placebo-controlled trials. Amongst others, an increased risk of fractures and falls was observed in patients treated with safinamide and concurrent use of anxiolytics and antihypertensive drugs and an increased risk of psychoses with amantadine use.

Significant safinamide interactions observed in the pooled Safety data base of main trials

Co-med, Adverse event	Incidence safinamide + co-med.	Incidence Placebo + co-med.	OR for safinamide vs placebo at Co-med.	OR for safinamide vs placebo without Co-medication	p-value#
Anxiolytics; fractures and falls	10 cases (14%)	0	14.62 (0.83, 256.06),	0.15 (0.02, 1.25)	0.0330
Antihypertensive: fractures and falls	9 (3%)	0	12.31 (0.71, 212.70)	0.15 (0.02, 1.25)	0.0015
Amantadine: psychoses	16 (7%)	6 (4%)	1.98 (0.76, 5.18)	0.58 (0.28, 1.21)	0.0435

By Breslow-Day testing for a difference in AE-by-treatment odds ratios between the With Co-medication and Without Co-medication groups. A Tarone adjustment was applied for all tests due to small numbers of adverse events in most categories; Co-med= co-medication

The analyses on pharmacodynamic interactions in the pooled dataset should be interpreted with caution, as there was no stratification for co-medication at baseline, and co-mediation was not kept constant over time. Thus a negative signal from this analysis could not completely exclude interactions.

When safinamide was added to L-DOPA, the incidence of dyskinesia increased, as may be expected as the dopaminergic load increases. However, most of them were of mild-moderate nature. For other MAO_B inhibitors like rasagiline, impulse control disorders have been reported, often in combination with dopamine agonists. Since all the main studies were performed in an add-on setting, it would be difficult to disentangle whether there is an additive risk of safinamide on its own, as there was no safinamide monotherapy comparator group available.

Safinamide inhibits serotonin-transporter enzyme (SERT) and may therefore display a serotonergic effect. Apparently, the combination with SSRI's did not induce serotonergic symptoms like dizziness, hypertension or neuropsychiatric events in the safinamide trials (117 subjects used both drugs). Nevertheless, a warning - but no contra-indication- was included in the SmPC for the use of SSRI's. This was supported, as serious adverse events have been reported for other MAO-B inhibitors used in combination with SSRI and other antidepressants.

2.6.4. Discussion and conclusions on clinical pharmacology

In general the pharmacokinetics of safinamide had been sufficiently characterized, however some deficiencies were noted in the dossier. PK interaction studies were still ongoing at the time of MAA to fulfill the information gap.

Safinamide is quickly and almost completely absorbed and extensively metabolized into several inactive metabolites. The primary route of elimination is via unspecified amidases, which were not fully identified at the time of assessment.

The potential for interaction of safinamide via CYP and P-gp is low, however the CHMP recommended that the company should still evaluate if safinamide may interact with BCRP substrates and submit the reports of several in vitro studies evaluating whether safinamide affects the function of transporters.

The CHMP recommended the below listed post-authorization measures in order to provide the necessary information to address the abovementioned deficiencies:

- *in vitro* substrate studies with safinamide for BCRP, OATP1B1, OATP1B3, OATP1A2, and OATP2B.
- *in vitro* performed studies to determine if NW-1153 is a substrate for OCT2, OAT1 and OAT3.
- *in vitro* performed studies to determine if NW-1153 inhibits OCT2, MATE1 and MATE2-K.
- *in vitro* performed studies to determine if safinamide is an inhibitor of OATP1A2 and 2B1.

Safinamide is a potent and specific MAO-B inhibitor. No dietary measures regarding tyramine-rich food, which is a substrate of MAO-A, were considered needed. The main effect of safinamide appears to be due to its MAO-B inhibiting properties. MAO-B inhibition is already expected to be optimal at the lower dose of 50 mg. This might explain why in the clinical studies no consistent dose effect was shown at dosages between 50-200 mg/day.

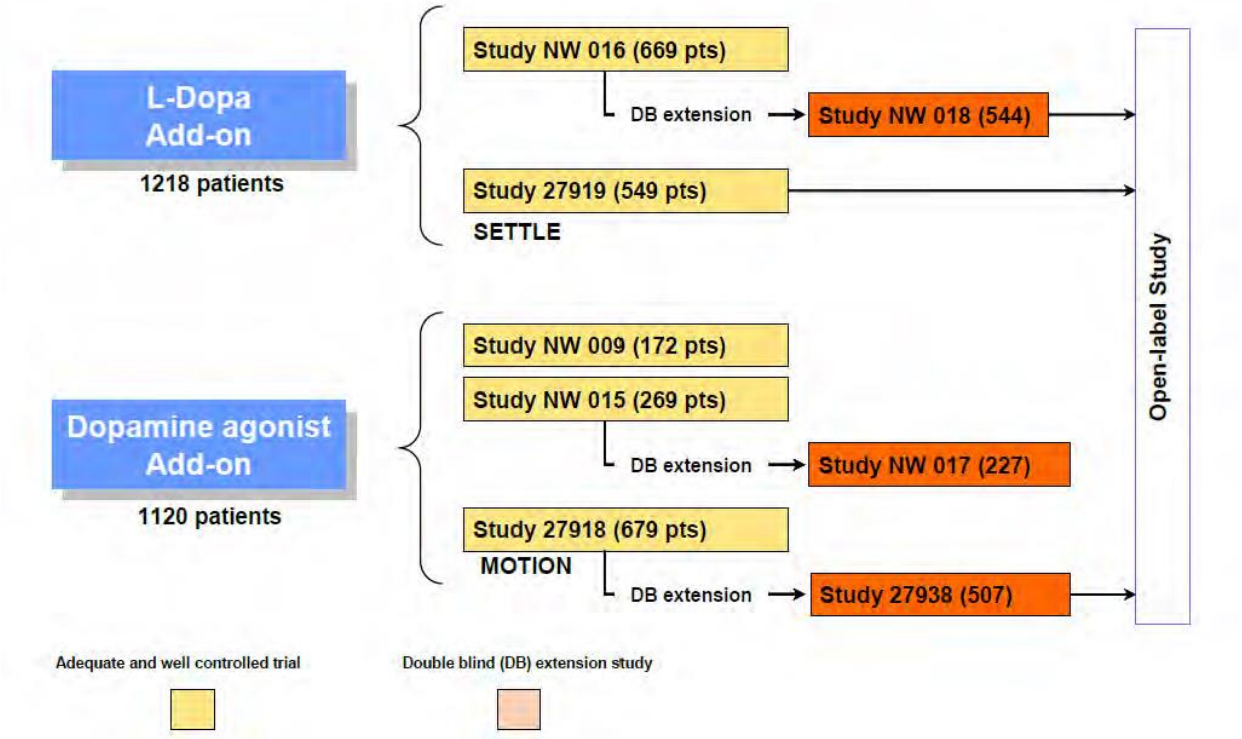
Safinamide also blocked sodium channels and modified glutamate release, which was initially theorized to have a favorable effect on dyskinesia symptoms. Based on the provided in-vitro data, it was debatable whether a relevant effect on the glutamate release could be expected at the therapeutic safinamide dose level of 50-100 mg per day. The role of sodium channel blockade in conditions like epilepsy and neuropathic pain is known but it has not been established in the treatment of Parkinson's Disease. It was postulated that modification of Na^+ channels may contribute to a favourable effect on dyskinesia symptoms. The ultimate proof to further test this hypothesis would have been a head-to-head comparison of safinamide to a `pure` MAO-B antagonist, but such a study was not presented. As discussed in the clinical efficacy part of this report, safinamide had no relevant effect on dyskinesia scores in the overall study population.

The claim in the SmPC that safinamide may act in late stage PD patients through both dopaminergic and non-dopaminergic mechanisms was therefore modified to reflect the above conclusions.

2.7. Clinical efficacy

Safinamide has been developed for the treatment of idiopathic Parkinson Disease (PD), as add-on therapy to dopamine agonists in early PD and as add-on therapy to L-DOPA and other anti-Parkinson agents in advanced PD patients. An overview of the overall clinical development plan is presented in the next Figure 3.

Figure 3 Overall clinical development plan



The DB Extension Study 27938 was interrupted by the former Sponsor, after the results of the prior MOTION Study became available.

The main features of the study design are also summarized in the tables (Table 6 and Table 7) below:

Table 6 Design features of the main studies in early Parkinson's disease

Study	Design	Study-arms ($N_{randomized}$/$N_{Completed}$)	Main endpoints / assessments
Add-on to dopamine-agonist monotherapy (PD < 5 years, H&Y stage I-III, no motor fluctuations)			
009 POC/Dose-finding 2001-2002 EU	Rd PC DB PA 12 weeks Patients with early Parkinson's Disease either de-NOVO or on dopamine-agonist monotherapy Age: mean 59.6 (SD 8.5)	0.5 mg/kg n=57/52 1 mg/kg n=57/48 Placebo n=57/49	***Primary*** Responders i.e. patients with 30% improvement on UPDRS motor score ***Other*** UPDRS III mean change, CGI-S, CGI-C, HAMD
015	Rd PC DB PA 24 weeks	50-100 mg n=90/81	***Primary***

2004-2006 Efficacy/safety EU/SA/India	Patients with early Parkinson's Disease on dopamine-agonist monotherapy Age: 58 (SD 8.5)	150-200 mg n=89/70 Placebo n=90/81 OD dose regime	Change in UPDRS motor score from baseline at week 24 ***Other*** Other UPDRS based outcomes, CGI-C, CGI-S, CogTest, Euro-QOL, HAMD, MMSE
MOTION 2009-2012 Efficacy/safety EU/SA/SAF/USA/Canada/India	Rd PC DB PA 24 weeks Patients with early Parkinson's Disease on dopamine-agonist monotherapy Age: 60.7 (SD 10.1)	50 mg n=227/199 100 mg n=227/2010 Placebo 225/201 OD dose regime	***Primary*** Change in UPDRS motor score from baseline at week 24 ***Other*** See under study 015 and PDQ-39
017 2005-2007 Efficacy/safety Long term extension of study 015 SA/EU/India	Double blind extension of study 015 till 18 months Patients from study 015 willing to enter study 017 Age 57.7 (SD8.5)	50-100 mg n=80/64 150-200 mg n=69/61 Placebo n=78/62 OD dose regime	***Primary*** Time to intervention / change in PD therapy[A] ***Other*** See under study 015

Legend: Can: Canada, *CGI-C: Clinical global impression of change, CGI-S: Clinical global impression of severity, DB: Double blind, EU: Europe, Euro-QoL:* European Quality of Life score, HAMD: Hamilton Depression scale, *H&Y: Hoehn Yahr stage,* MMSE: Minimal Mental State Examination, NZ: New Zealand**,** *PA: Parallel group study, PC: Placebo-controlled, PD: Parkinson's Disease ,* PDQ-39: Parkinson's disease questionnaire, *POC: Proof of concept , SA: South-America, SAF: South-Africa, Rd: Randomised, UPDRS: Unified Parkinson's Disease Rating score.*

[A]Time to change in background PD therapy is defined as time form entry study 015 to intervention that is increase in dopamine-agonist **or** addition of L-dopa or other Anti-Parkinson **or** discontinuation due to lack of efficacy

Table 7 Design features of the main studies in late Parkinson's disease

Study	Design	Study-arms ($n_{RD}/N_{Completed}$)	Main endpoints / assessments
Add-on to L-dopa w/wo concomitant Anti-Parkinson medication (PD > 5 years, H&Y stage I-IV and motor fluctuations e.g > 1.5 hour off)			
016	Rd PC DB PA DB 24 weeks	50 mg/day n=223/222	***Primary*** Mean daily ON time

2007-2008 EU/India Efficacy/safety Fixed Dose	Patients with Parkinson's Disease and motor fluctuations on a stable doses of L-dopa and/or other dopaminergic medication and/or anticholinergic medication Age 34 - 80 yrs	100 mg/day n=224/185 Placebo n=222/197	without troublesome dyskinesias over 18 hours ***Other*** Decrease in OFF time, UPDRS outcomes in ON, CGI-C, CGI-S, CogTest battery, Dykinesia rating scale, HAMD-17, MMSE, PDQ-39.
SETTLE 2009-2012 Asia/EU/USA/CanAustralia/NZ Efficacy/safety Flexible dosing	Rd PC DB PA DB 24 weeks Patients with Parkinson's Disease and motor fluctuations on a stable doses of L-dopa and/or other dopaminergic medication and/or anticholinergic medication Age 40 - 80 yrs	50-100 mg/day n=274/245 Placebo n=275/237	***Primary*** Mean daily ON time with no or only minor dyskinesias ***Other*** Decrease in OFF time, UPDRS outcomes in ON, CGI-C, CGI-S, CogTest battery, Dykinesia rating scale, HAMD-17, MMSE, PDQ-39, EQ-5D.
018 2007-2010 EU/India Efficacy/safety	Double blind extension of study 016, 18 months Patients from study 016 willing to enter study 018	50 mg/day n=189/148 100 mg/day n=180/150 Placebo n=175/142	***Primary*** Mean change in DRS in ON time compared to study 016 baseline ***Other*** Change in ON time, responder rate[B], Other UPDRS derived variables change in L-dopa dose, change in PD medication, CGI–C, CGI–S, H &Y staging, HAMD-17, MMSE, PDQ-39, Cogtest battery.

[B]Responder was defined as a subject with an improvement in ON time with at most minor dyskinesia, no increase in troublesome dyskinesia and lack of worsening (≤ 30 minutes)

2.7.1. Dose response study(ies)

Study 009 – Dose response

Study 009 is a randomized, double- blind, dose finding, parallel-group study. PD patients without motor fluctuations were included. Both treatment naïve (de-novo) and patients on a stable dose of DA-agonist were eligible.

172 PD patients were randomly assigned to 1 mg/kg dose, 0.5 mg/kg dose or placebo, for a period of 12 weeks. Subjects on a stable dose of a single DA-agonist were allowed to maintain their treatment in the study. Primary endpoint was ≥ 30% improvement in the UPDRS III motor symptoms at 12 weeks.

Mean safinamide dose was 78.1 mg (range 40-91kg) for the 1 mg/kg group, and 34.4 mg (16-40.5 mg) for the 0.5 mg/kg group.

Baseline mean UPDRS score was 16.6 (SD 7.6), 15.9 (7.0) and 17.5 (7.9) for the 0.5 mg/kg, 1 mg/kg, and Placebo group, respectively.

Responder rates defined as ≥30% improvement in UPDRS III motor symptoms, were significantly higher for the 1 mg/kg dose compared to placebo but not for the 0.5 mg/kg dose (as assessed by logistic regression taking subgroup and center into account, see Table 8 below). The overall effect was however clearly driven by the subgroup of patients on DA-agonist monotherapy. No effect was shown for the de-novo subgroup. Furthermore, improvement UPDRS- motor scores from baseline was in favor of both active treatments in combination with a dopamine-agonist.

Table 8 Responder rate (% of patients) at final visit (ITT cohort, N=167)

	Placebo N=56 n (%)	Safinamide 0.5 mg/kg N=55 n (%)	Safinamide 1 mg/kg N=56 n (%)	Safinamide 0.5 mg/kg versus placebo (p-value)*	Safinamide 1 mg/kg versus placebo (p-value)*
All patients	12 (21.4)	17 (30.9)	21 (37.5)	0.143	0.018
Single DA	7 (20.6)	12 (36.4)	16 (47.1)	0.195	0.006
De-novo	5 (22.7)	5 (22.7)	5 (22.7)	0.874	0,925
Responders#	12 (21.4)	17 (30.9)	21 (37.5)	0.132	0.016

#defined as improvement of at least 30% in UPDRS III from baseline to final visit (Visit 9 or early study termination)
*logistic regression

Based on the overall higher response on motor symptoms in the subgroup of patients treated with DA-agonists, drug-development was continued as add-on therapy to DA-agonist, and not as monotherapy.

Dose-finding was further evaluated in the confirmatory Phase III trials, where fixed oral doses of 50-200 mg daily were applied.

2.7.2. Main study(ies)

2.7.2.1. Early stage Parkinson Disease add-on to dopamine agonist

2.7.2.1.1. Study 015 (including extension study 017), and the MOTION Study.

Methods

Study 015 and the MOTION Study concern randomized, multi-center, multinational, placebo-controlled, multiple dose, parallel group studies in Parkinson patients without motor fluctuation. Duration of the double-blind period was 24 weeks. Safinamide was given on top of dopamine-agonist monotherapy.

Main inclusion criteria specified patients with a diagnosis of PD of less than 5 (3 for MOTION) years duration, and a Hoehn-Yahr Stage of I-III, who were receiving treatment with a single dopamine agonist at a stable dose for at least 4 weeks prior to screening.

During the 24-week Treatment Period, the dopaminergic background therapy of DA-agonist was kept constant. However, dose adaptation, change to other anti-Parkinson medication, was allowed if absolutely necessary to treat a worsening of the patient's condition. Decreases in the DA-agonist dose were also permitted if based on the occurrence of AEs.

Main differences between these studies concern the active dose arms and number of subjects. The dose arms in study 015 were 50 -100 mg and 150-200 mg safinamide once daily. Patients in study 015 were titrated up to the maximal tolerated doses within their dose range arm. De facto, more than 90% of the patients received the maximal dose allowed in the range, i.e. 100 mg/day or 200 mg/day. The dose arms in the MOTION study were 50 mg or 100 mg safinamide once-daily. The total number of subjects was 269 in study 015 and 679 in the MOTION study.

Outcomes

Primary outcome in both study 015 and the MOTION study was the change in UPDRS-III motor score at week 24 as compared to baseline.

The secondary endpoints of study 015 and the MOTION study were the same although the order of importance differed : CGI-responders rates, UPDRS-III responders (≥ 20% or ≥ 30% improvement from baseline), MMSE, Euro-Quality of Life (Euro-QOL), UPDRS-IV (Complication of Therapy) and Cogtest, a test battery of cognitive function.

Statistical methods

The main analysis set was the ITT population in both studies.

In study 015, the change in UPDRS III score was analyzed using a mixed model analysis of covariance with baseline UPDRS III score as covariate, treatment, visit and the treatment visit interaction as fixed effects, and country as random effect. The analysis was performed without imputation of missing data. Four sensitivity analysis based on imputation were used (Last Observation Carried Forward (LOCF), Retrieved Drop Out analysis (RDO), Observed Case (OC) and Observed Case and Retrieved Drop Outs (OC and RDO) for the handling of missing values. The RDO population incorporated all patients who discontinued study-treatment prematurely, but returned for their efficacy assessment in the designated window period. For secondary continuous outcomes, an ANCOVA was used with the Baseline value for each variable as covariate and treatment group and country as main effects. For dichotomous secondary endpoints the Cochran Mantel-Haenszel method weighted by country was used.

In the MOTION study, the primary endpoint was analyzed using an analysis of covariance (ANCOVA) model on the change from Baseline to Week 24, with fixed effects of treatment and region and the

baseline value of the UPDRS III score as covariate. The treatment-by-region interaction and treatment-by-UPDRS Baseline interaction were evaluated. If the interaction was statistically significant ($p < 0.1$), then further subgroups analysis using a nonparametric ANCOVA main model was conducted. The primary analysis of the change in UPDRS III score was based on the so-called "On-Treatment Approach" that is only the On-Treatment efficacy data were used for analysis. Efficacy assessment of subjects whose treatment was withdrawn, or whose background anti-Parkinson medication was changed were not taken into account. Missing values for the week-24 endpoint were imputed by a Last Observation Carried Forward (LOCF) approach using the last post-Baseline On-Treatment value. The same ANCOVA model used for the primary efficacy parameter was used for the continuous secondary clinical parameters. Dichotomous endpoints were analyzed using a logistic regression model with treatment and region effects.

A hierarchical procedure was pre-specified used for the comparison of the primary parameter between each safinamide dose to placebo. First, the highest safinamide dose was compared with placebo. If this comparison was found to be statistically significant, then the lowest safinamide dose was compared with placebo. In case the result for the highest dose was not significant the comparison of the safinamide 50-mg/day dose to placebo was not performed. In the MOTION study testing of the key secondary efficacy analyses was performed in a pre-specified order with key secondary endpoints being UPDRS-II (ADL), CGI-C responders, PDQ-39, Cogtest-PD-battery. All secondary endpoints tested sequentially, first for safinamide 100 mg/day versus placebo, and then for safinamide 50 mg/day versus placebo once all parameters completed the 100-mg/day test successfully. The test for the next parameter/dose was only to proceed if the test for the preceding parameter was significant.

In the MOTION Study, Sensitivity analyses of the primary endpoint were performed with different analyses datasets (Completer or Per Protocol), the analysis approach (On-Treatment or Observed Case), and the statistical modeling approach (MMRM). In the "On-Treatment Approach", subjects whose treatment was withdrawn, or background anti-Parkinson medication was changed, were not taken into account.

Results of Study 015 and the MOTION Study

Study Population

About 38% of the patients from study 015 came from India, 33% from W-Europe, and 29% from South-America.

About 45% of the study population in the MOTION study came from Europe, 30% from Latin America, 15% from the US, and 10% from Asia.

In the next Table 9 the number of subjects, participant flow, and main baseline features of study 015 and the MOTION study are presented:

Table 9 Study 015 - MOTION study: number of subjects, participant flow, main baseline features

	STUDY 015			**MOTION STUDY**		
Time window	21-12-2004 ; 23-01-2006			27-03-2009 ; 23-02-2012		
n-screened	293			871		
Study arm	**150-200 mg/day**	**50-100 mg/day**	**Placebo**	**50 mg/day**	**100 mg/day**	**Placebo**
n-randomised	90	90	90	227	227	225

n-ITT	89[A]	90	90	226[B]	227	225
Drop-out due to	19	9	9	28	17	27
Adverse events	5	3	2	3	5	12
Lack of efficacy	2	0	0	10	3	2
Mean age (sd)	58.5 (11.7)	56.5 (11.3)	57.3 (10.8)	60.5 (10.2)	60.4 (9.8)	61.2 (10.3)
Duration PD (x, sd)	NR	NR	NR	1.9 (1.4)	1.9 (1.4)	1.7 (1.4)
H &Y stage (median)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)	2 (1-3)
UPDRS-III score$_L$	19.3	22.0	20.7	21.0	18.9	19.8
Dose study medication						
Dose level endpoint	91%	95.6%	91.1%	NA	NA	NA
Modal dose	100 mg	200 mg	NA	NA	NA	NA
Compliance	86.5%	92.2%	90.0%	98.4%	99.1%	98.8%
Comorbidity						
Cardiac disorder	12.4%	6.7%	10.0%	7.0%	4.0%	6.7%
Hypertension	30.3%	32.2%	32.2%	41.0%	34.4%	47.1%

NA=not applicable, NR=not reported

Most frequent dopamine agonist used was ropinirole (around 45% study 015) and pramipexole (around 55% in the MOTION study).

In Study 015, routine monitoring of PK samples revealed that in 79 out of 90 subjects [88%] assigned to placebo-treatment tested positively for safinamide at various time points throughout the study, and wide-spread over the treatment centers. A root cause analysis, which was performed in the bio-analytical laboratory, excluded that this was due to a bio-analytical failure. Analysis indicated that this probably occurred during filling of the bulk bottles with either placebo- or safinamide-capsules. No further concerns were raised on this issue, as the safinamide plasma levels in the contaminated placebo-controls were a fraction of the levels that were achieved at steady-state of safinamide, and as the Test drug safinamide was not favoured by a potential higher placebo control.

Routine monitoring in the MOTION trial did not provide evidence of contaminated placebo samples.

Efficacy

The results for the primary endpoint, improvement in UPDRS-III score, and main secondary endpoints for study 015 and the MOTION study are presented the next Table 10. Overall the change in UPDRS-III score from baseline was modest.

Table 10 Main outcomes study 015/MOTION study

	STUDY 015			**MOTION STUDY**		
Study arm	**50-100 mg/day**	**150-200 mg/day**	**Placebo 0 mg/day**	**50 mg/day**	**100 mg/day**	**Placebo 0 mg/day**

	n=90	n=89	n=90	n=227	n=227	n=227
UPDRS III score						
Baseline	22.0	19.3	20.7	21.0	18.9	19.8
Week 24 or Endpoint	-6.0	-3.9	-3.6	-1.60	-1.9	-0.95
Difference placebo	-1.9	-0.4		-0.65	-1.04	
95% CI	-3.7 ; -0.1	-2.3 ; 1.4		-1.8 ; 0.48	-2.2 ; 0.10	
p-value	*0.042*	*0.65*		*0.26*	*0.07*	
Methods	Mixed linear model, unstructured covariance model. All covariance structures were tested, but the unstructured covariance model had the best fit·			ANCOVA) with treatment and region as fixed effects and the Baseline value of the UPDRS Section III score as the covariate. Treatment group comparisons were based on evaluating the differences in Type III least squares (LS) mean changes from the ANCOVA main model.		
Change in Dopamine-agonist medication during DB	8.9%	4.5%	5.6%	2.6%	2.2%	3.5%
UPDRS-II score						
Baseline	8.2	7.3	8.1	7.38	6.7	6.88
Endpoint	-2.2	-1.4	-1.2	-0.44	-0.50	-0.05
p-value vs. Placebo	*0.025*	*0.276*		*0.142*	*0.085*	
UPDRS-**30%** responders	38.2%	36.8%	24.7%	26.9%	24.7%	20.4%
p-value vs. Placebo	*0.059*	*0.084*		*ns*	*ns*	
UPDRS-**20%** responders	49.4%	47.1%	33.7%	-	-	-
p-value vs. Placebo	*0.043*	*0.064*				
CGI-responders	62.2%	59.3%	48.9%	48.0%	45.8%	40.4%

p-value vs. Placebo (any improvement)	*0.08*	*0.19*		*0.09*	*0.23*	
PDQ-39 Index						
Baseline	NA	NA	NA	18.5	17.2	17.0
Change at week 24	NA	NA	NA	-1.00	-2.03	-0.31
p-value vs. Placebo				*0.399*	*0.036*	

NA=not applicable, ns=non-significant (95% CI of the differences)

Study 015:

Primary endpoint

The comparison of -0.4 points improvement in UPDRS-III scores for the 150-200 mg dose group versus placebo was not statistically significant (p-value = 0.65). The improvement for the 50-100 mg dose group was larger as compared to the 150-200 mg dose group (-1.9 points, 95% CI -3.7, -0.1). The value for the comparison versus placebo - without any adjustments for multiple comparisons that should have been applied in this case - revealed a p-value of 0.0419.

Secondary and tertiary endpoints

There were some changes in the secondary endpoints like UPDRS-II and UPDRS-20% improvement responders in favor of the 50-100 mg dose that were statistically significant without adjustment for multiplicity. No statistically significant effect was observed the other secondary endpoints, or for any of these outcomes for the 100-200 mg dose level. There were no significant differences between study groups regarding tertiary endpoints like depression (HAMD 17-item total score), UPDRS Section I (Mentation, Behavior and Mood) scores, UPDRS Section IV (Complication of Therapy). MMSE (Mini-Mental State Examination) was actually significantly worse for the High Dose safinamide group compared to placebo (p=0.028), but no significant effect was shown for the Low Dose for this outcome. There were no significant differences for QOL scores between active treatment and placebo.

MOTION study:

Primary endpoint

The comparison of -0.65 points of improvement in UPDRS-III scores for the 50 mg dose group versus placebo was not significant. For the 100 mg dose group, comparison of -1.04 points of improvement was neither statistically significant different from placebo.

Secondary endpoints and tertiary endpoints

There were no significant differences between study arms with respect to the Cogtest® PD Battery test (Strategic Target Detection Test and Auditory Numbering Sequence). The subsequent exploratory analysis of the other supporting cognitive endpoints showed no statistically significant safinamide versus placebo differences for either of the two doses for any of the ANS, Spatial Working Memory Test, or Tower of London measures. Of all the STDT endpoints, only the Two Shape Total Errors showed a statistically significant difference for the safinamide 50-mg/day versus placebo comparison, but not for the safinamide 100-mg/day group.

Several of the other secondary endpoints did show statistically significant differences for the safinamide 100-mg/day group versus placebo comparison. These included the following: CPTF - Proportion correct all conditions, Sum Correct Congruent, Sum Correct Incongruent, Sum Correct Neutral, Pr and Proportion incorrect all conditions. These differences were not seen in the safinamide 50 mg/day versus placebo comparisons.

Sensitivity analyses

In general the ancillary analyses gave the same picture. Two observations are worth mentioning:

- In the MOTION study region appeared to be a relevant factor in the primary analyses as a subgroup analyses based on region showed statistical significant results for West-Europe, but reverse outcomes for Eastern-Europe:

Table 11 Results by region in the MOTION study

All Subjects	Safinamide 50 mg/day			Safinamide 100 mg/day		
Region(s)	N	LS Mean (SE) Diff vs. Placebo [a]	p-value	N	LS Mean (SE) Diff vs. Placebo [a]	p-value
All Regions [b]	227	−0.65 (0.58)	0.259	227	−1.04 (0.58)	0.073
Asia	25	1.82 (1.54)	0.2406	24	−1.02 (1.58)	0.5199
Eastern Europe	47	1.32 (1.44)	0.3636	48	0.25 (1.43)	0.8617
Western Europe	56	−2.17 (1.04)	**0.0375**	56	−2.47 (1.03)	**0.0182**
Latin America	67	−1.81 (1.09)	0.0986	67	−0.71 (1.09)	0.5147
North America	32	−0.18 (1.46)	0.8998	32	−1.28 (1.46)	0.3830
N. America + W. Europe	88	−1.51 (0.86)		88	−2.00 (0.86)	**0.0207**
N. America + W. Europe + Asia	113	−0.77 (0.75)	0.3041	112	−1.78 (0.75)	**0.0189**
N. America + W. Europe + Asia + Latin America	180	−1.16 (0.62)	0.0628	179	−1.38 (0.62)	**0.0270**

Abbreviations: ANCOVA, analysis of covariance; ITT, intent to treat; LOCF, last observation carried forward; LS, least squares; SE, standard error; UPDRS III, Unified Parkinson's Disease Rating Scale – Section III.
[a] Parametric ANCOVA model is based on the change from Baseline to endpoint with fixed effects for treatment and region and Baseline value as covariate. All p-values, LS means and confidence intervals are calculated from the ANCOVA model.
[b] "All Regions" includes North America, Western Europe, Asia, Latin America, and Eastern Europe .

- Further, in retrospective it was discovered that 11 subjects in the MOTION study used two DA-agonists instead of one at baseline, which was considered as a violation of the inclusion criteria. Post-hoc exclusion of these subjects from the analysis resulted in a statistically significant difference in favour of the 100 mg/day dose group (see Table 12):

Table 12 UPDRS III score- Results from the MOTION study

	MOTION STUDY		
Study arm	**50 mg/day** n=223	**100 mg/day** n=221	**Placebo** n=222
UPDRS III score			
Baseline	20.8	18.9	19.8
Change at 24 weeks	-1.59	-2.09	-0.89
p-value	*0.23*	*0.04*	

Study 017

Methods

Study 017 concerned an extension of study 015 for another 12 months. Patients of study 015 who were willing to enter study 017 remained in their original study arm. Placebo and double blinding was maintained. Anti-Parkinson co-medication could be adapted. The dose of the DA-agonist could be increased or decreased, and L-Dopa, a second DA-agonist or any other Anti-Parkinson medication could be added, throughout the study.

Primary efficacy endpoint was time to Intervention, i.e. the time from first administration of the study medication to change in background Parkinson co-medication defined as an increase in the dose of DA-agonist as compared to baseline or addition of another DA-agonist, Levodopa, or some other anti-Parkinson medication or discontinuation due to lack of efficacy. Secondary endpoints were the same as in study 015.

All statistical analyses were performed for pooled data of the two safinamide dose groups (50-100 mg and 100-200) mg. For the primary endpoint, a Cox regression model was applied, adjusting for explanatory variables in this model like treatment, duration of Parkinson's disease, H&Y stage, region, baseline UPDRS score, gender and age.

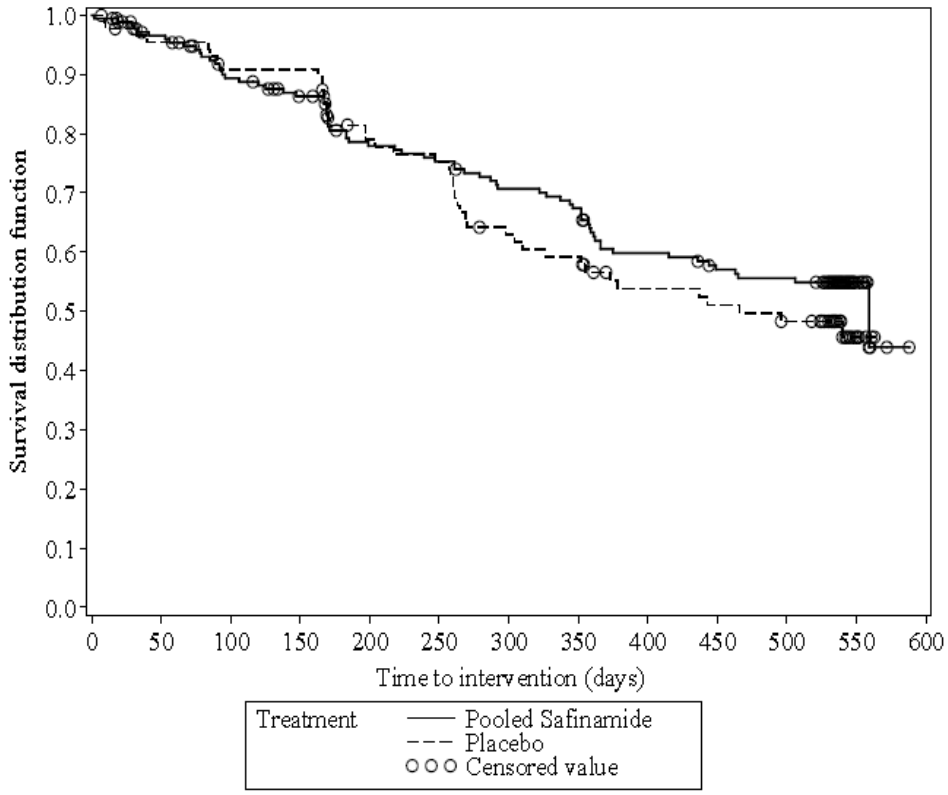
The secondary endpoints that were analyzed for a selected group - patients randomized at baseline of the prior Study 015, but did not continue the extension study 017, were excluded from these analyses.

Results

The retention rates were high, i.e. 76.6%, 88.9% and 86.7% of the subjects on 50-100 mg/day, 100-200 mg/day or placebo in study 015 entered study 017.

For time to Intervention, there was no significant difference between active treatmentand placebo. A Kaplan-Meier curve is presented in the next Figure 4. The median time to intervention was 559 days for the pooled safinamide groups versus 466 days in the placebo group (p-value Log Rank Test 0.3342).

Figure 4 Primary endpoint Study 017: Free of Intervention

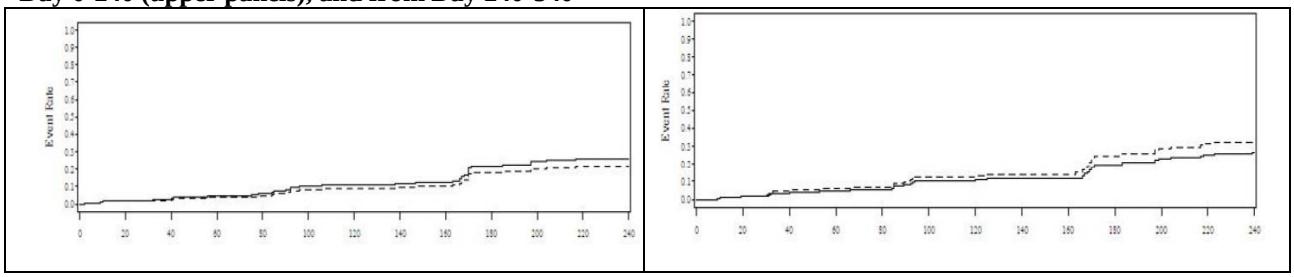


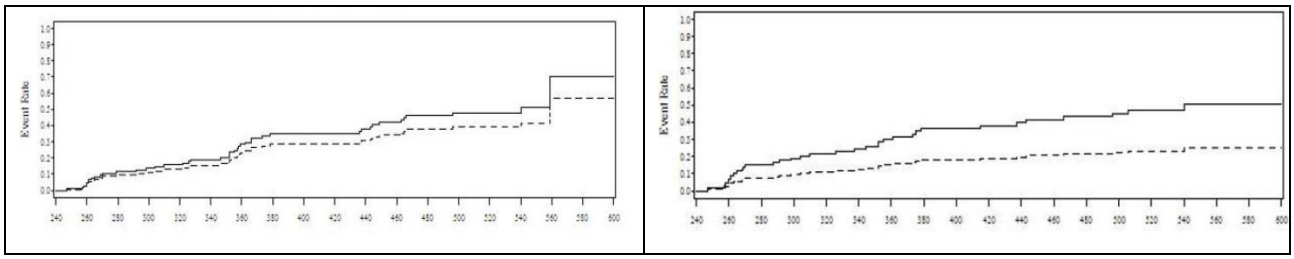
For the secondary endpoints also none of the differences were statistically significant in the pooled safinamide analyses. The rate of interventions was 39.7% in the Safinamide group, versus 47.8% in the Placebo group (difference 8.1%, 95% CI -20.4, 4.3)

Retrospectively in the evaluation of time to intervention, it was suggested that the Hazard Ratio of 0.83 (CI 95% = 0.57-1.21) was not constant throughout the period. Moreover, the event rate was much lower than expected in both groups. Therefore, so-called Landmark analyses were performed. The follow-up time was split into two time-windows for which the proportional hazard assumption was supposed to hold i.e. 0-240 and 240-540 days. Moreover the study arms were analyzed separately.

There was no significant difference in the proportion of interventions in the 50-100 mg/day dose group for the first 240 days. For the 50-100 mg dose group, there was a lower rate (25%) of intervention as compared to placebo (51%) in the period from 240 to 540 days (p value < 0.05, Cox Regression Model). The landmark analyses for the 100-200 mg/day dose group was inconclusive (Figure 5).

Figure 5 Landmark analyses of time to Intervention High Dose (left panels) & Low Dose (right panels), from Day 0-240 (upper panels), and from Day 240-540





For the secondary endpoints, additional analyses (Mixed Linear Analysis for High and Low Dose groups separately) were done for Responder Rates, using two additional definitions (> 20% and > 30% improvement in UPDRS III (Figure 6).

Figure 6 Post-hoc analyses Mixed Linear Analyses of Responder Rates (> 20% and > 30% improvement in UPDRS III) in High and Low Dose Group.

Variable	High Dose	Low Dose	Placebo
Responder (≥20 % decrease)	39.1 (27/69)	55.0 (44/80)	44.9 (35/78)
Responder (≥30 % decrease)	26.1 (18/69)	41.3 (33/80) ‡	24.4 (19/78)

‡ P-value = 0.0249 for comparison vs. Placebo

Finally the UPDRS I-IV, CGI, and Quality of Life (QOL) were analyzed for each subgroup separately, using both Mixed Linear Analysis and ANCOVA (LOCF) for the following categories:

"ON Treatment" - Analysis: patient's data are censored at the time of rescue medication intake (Intervention);

"ON and OFF Treatment" - Analysis: all available data are analyzed, regardless of rescue medication intake (Intervention).

The results are presented in the below Table 13:

Table 13 Mixed Linear Analyses of UPDRS Sections I-IV, CGI, and QoL in High and Low Dose

		Safinamide High Dose			Safinamide Low Dose		
		95% CI	SE	p value	95% CI	SE	p value
UPDRS I	On treatment	-0.54; 0.65	0.25	ns	-0.47; 0.69	0.25	ns
	On/off treatment	-0.46; 0.42	0.21	ns	-0.31; 0.54	0.21	ns
UPDRS II	On treatment	-1.86; 0.50	0.60	ns	-2.24; 0.09	0.59	ns
	On/off treatment	-1.69; 0.47	0.55	ns	-1.83; 0.27	0.53	ns
UPDRS III	On treatment	-4.75; 0.65	1.37	ns	-5.69; -0.36	**1.36**	**0.0264**
	On/off treatment	-3.34; 1.32	1.19	ns	-4.92; -0.38	**1.16**	**0.0222**
UPDRS IV	On treatment	-0.17; 0.28	0.12	ns	-0.34; 0.12	0.12	ns
	On/off treatment	-0.25; 0.18	0.11	ns	-0.29; 0.13	0.11	ns
CGI-S	On treatment	-0.37; 0.15	**0.13**	ns	-0.43; 0.09	**0.13**	ns
	On/off treatment	-0.28; 0.17	0.12	ns	-0.40; 0.04	0.11	ns
QOL	On treatment	-1.17; -0.15	0.26	**0.0113**	-1.06; -0.06	0.26	**0.0291**
	On/off treatment	-1.05; -0.12	0.24	**0.0143**	-1.0; -0.09	0.23	**0.0191**

CGI = Clinical Global Impression; QOL = Quality of Life; UPDRS = Unified Parkinson's Disease Rating Scale.
Source: Table 2.3.1a–b; Table 2.3.2a–b; Table 2.3.3a–b; Table 2.3.4a–b; Table 2.3.5a–b; Table 2.3.6a–b

2.7.2.2. Late stage Parkinson Disease add to L-dopa with / without other Anti-Parkinson medication

The main studies to support this indication are study 016 and the SETTLE study. In addition, there was double-blind extension of Study 016 i.e. Study 018 which is presented separately.

2.7.2.2.1. Study 016 and the SETTLE study

Both studies concerned a randomised, multi-centre, multinational, placebo-controlled, multiple dose, parallel-group study in patients with Parkinson's disease with motor fluctuations. Duration of the double blind was 24 weeks. Safinamide was given on top of L-dopamine, with or without or other anti-Parkinson medication. Total number of subjects was 669 in Study 016, and 549 in the SETTLE study. Main difference between Study 016 an the SETTLE Study was that in Study 016 there were two fixed dose arms (safinamide 50 mg/day, safinamide 100 mg/day), whereas in the SETTLE Study there was a flexible dose range 50-100 mg/day.

Main inclusion criteria concerned patients between 30-80 years of age, with a diagnosis of idiopathic PD of more than at least 5 years (study 16) or 3 years (SETTTLE), a Hoehn and Yahr stage of I-IV during an OFF phase, and motor fluctuations with >1.5 hours of OFF time during the day. Patient must have been receiving treatment with a stable dose of L-dopa (3-10 doses per day of any L-dopa preparation) and may have been receiving concomitant treatment with stable doses of a DA-agonist and/or an anticholinergic and/or amantadine and/or a COMT inhibitor at the screening visit.

Endpoints

The primary efficacy variable in both studies was the change in daily ON time without troublesome dyskinesia at 6 months.

An OFF phase was defined as lack of mobility (bradykinesia, or akinesia), whereas in an ON phase, the patient was functioning as well as can be expected for that patient, irrespective of whether he or she was having dyskinesias. This information was collected on the diary on the 5 days (study 016) or 3 days (SETTLE) preceding the scheduled visit, and the last 2 days of recording were used for data analysis purposes.

The main secondary endpoints concerned responder (30% improvement in ON-time), decrease in total daily OFF time, change in UPDRS-III score in the ON-phase, CGI-C responder rates, Cogtest , UPDRS-II, DRS (Dyskinesia Rating Scale) score during ON-time, change in PDQ-39 score (a physical and mental functioning score specifically designed for Parkinson's disease), EQ-5D (a QOL scale) , and L-dopa dose.

Study 016:

Analyses of the primary endpoint

The primary analysis set in study 016 was the ITT population. The primary efficacy variable was analyzed using a mixed linear model with treatment, center and the treatment-by-visit interaction as fixed effects and baseline ON time as a covariate.

The multiplicity issue for treatment groups was handled by using a sequence of comparisons approach. The safinamide 100-mg/day group was tested first, and only if there was a significant difference compared with the placebo group was the safinamide 50 mg/day group versus the placebo group to be tested.

Sensitivity analyses using two mixed linear model analyses were performed on the ITT population: ON-treatment analysis and ON-and-OFF treatment analysis. In the ON-treatment approach, patients' data were censored at the time of rescue medication intake or occurrence of RDO. In the ON-OFF approach, all available data were analyzed regardless of the intake of rescue medication and included RDO data. Rescue medication was defined as an increase in the total daily dose of the background PD therapy by 20% or the addition of a new anti-Parkinsonian medication.

Analyses of the secondary endpoints

The secondary efficacy variables were evaluated in a hierarchical manner. Each of the variables was analyzed sequentially as long as a significant difference between the safinamide 100 mg/day group versus the placebo group was detected. If the difference between the safinamide 100 mg/day and placebo groups was not statistically significant for a particular variable, statistical tests on subsequent variables were performed only to obtain nominal p-values, but not for hypothesis testing. Analyses were performed on the ITT population, using the on-treatment approach and with LOCF imputation of missing data. The secondary efficacy analysis included the following parameters, ordered according to the hierarchical analysis approach decrease in total daily OFF time, as measured in the diary card—change from Baseline to endpoint, UPDRS III at ON, CGI–C, Change in cognition Cogtest, Decrease in mean OFF time following first morning dose of levodopa, Improvement in the DRS at ON, UPDRS II at ON, CGI-S and mean percentage change in levodopa dose.

SETTLE:

Analyses of the primary endpoint

The primary analysis of the primary endpoint (daily ON time) was performed based on the ITT Population using the On-Treatment Approach. This primary endpoint was analysed using an analysis of covariance (ANCOVA) model on the change from baseline to Week 24, with treatment and region effects and the baseline value of the daily ON time as the covariate.

In addition to the primary analysis with the ANCOVA main model, supportive analysis using a mixed effects repeated measures model (MMRM was used to evaluate treatment, time, and treatment-by time interaction effects on the change from baseline to post baseline visits in daily ON time. Other sensitivity analyses of the primary endpoint were performed based on a combination of the analysis population (ITT, MITT, Completer, or Per Protocol), the analysis approach (On-Treatment or Observed Case), and the statistical modelling approach (ANCOVA or MMRM)

Analyses of the secondary endpoints

Testing of the key secondary efficacy analyses was performed in a hierarchical fashion i.e. daily OFF time, UPDRS III score in ON, UPDRS-II in ON, CGI-C-improvers and change in PDQ-39 score. Each of the above key efficacy endpoints was analyzed sequentially as long as a significant difference between the safinamide group versus placebo group was seen. The same ANCOVA model used for the continuous secondary clinical parameters with the baseline value as a single covariate. CGI-C-responders were analysed using a logistic regression model with treatment and region effects.

Results study 016 /SETTLE study

Population

Study 016 (Table 14) was conducted at 35 sites in India, 7 sites in Italy, and 10 sites in Romania, with a target enrollment of 18 patients per center.

The SETTLE study was conducted at study centers in India, Malaysia, South Korea, Taiwan, Thailand, Estonia, Slovakia, Canada, the United States, Australia, Austria, Belgium, France, Germany, Hungary, Israel, the Netherlands, New Zealand, Spain, Switzerland, and the United Kingdom.

In the next Table 14 the number of subjects, participant flow, main baseline features of study 016 and the SETTLE study are presented.

Mean age was about 60 years and duration of Parkinson's disease ranged from 8-9 years. Patients were in an ON phase about half of the waking time of 18 hours. OFF phase was about 5 hours. There was no apparent difference in distribution of baseline features over the study arms

In the SETTLE study the majority of subjects on active treatment received the 100 mg dose, i.e. around 80% at 24 weeks.

Table 14: Study 016/ SETTLE Number of subjects, baseline features flow

	STUDY 016			**SETTLE STUDY**	
Time window	13-01-2007 ; 28-10-2008			05-03-2009 ; 23-02-202	
n-screened	900			851	
Study arm	**50 mg/day**	**100 mg/day**	**Placebo**	**50 -100 mg/day**	**Placebo**
n-randomised	223	224	222	274	275
n-ITT	223	224	222		
n-completed	202	195	197	241	237
Change PD medication < 24 weeks				4.0%	7.6%
Mean age (sd)	60.1 (9.65)	60.1 (9.19)	59.4 (9.41)	61.7 (9.0)	62.1 (8.9)
Female	29.6%	27.2%	27.9%	37.6%	40.7%
Duration PD (y)	7.94	8.15	8.29	8.9	9.0
H &Y stage (median)	3.0	3.0	3.0	2.50	2.50
UPDRS-III score at BL	27.3	28.3	28.7	22.3	23.3
Time ON without troublesome dyskinesia BL (HR)	9.37	9.52	9.30	9.30	9.06
L-dopa dose (mg/day)	622.87	572.49	619.20	760.8	792.3
Dopa-agonists	63.7%	57.1%	61.7%	75.5%	73.1%
Anticholinergics	33.2%	38.8%	39.2%	16.8%	17.8%
Other PD co-medication	12.1%	11.2%	13.5%	31.0%	29.5%

[A]One death in each study arm, B four deaths

Primary outcomes, Study 016 and SETTLE Study

In study 016, the mean total daily ON time without troublesome dyskinesia over 18 hours increased over time for each of the 3 treatment groups. At the end of the study at week 24 the mean change from Baseline was 0.97 (SD 2.38) hours for the placebo group, 1.37 (SD 2.75) hours for the safinamide 50 mg/day group, and 1.36 (SD 2.63) hours for the safinamide 100 mg/day group, respectively. The mean change from baseline was 0.72 hours for placebo, 1.23 hours for safinamide 50 mg/day and 1.28 hours for safinamide 100 mg/day. Difference versus placebo was statistically significant for both dose groups i.e. 0.51(95% CI 0.07, 0.94) hours for the safinamide 50 mg/day group [p = 0.023] and 0.55 (95% CI 0.12, 0.99) hours for the safinamide 100 mg/day group [p = 0.013]). For details see Table 15 below.

In the SETTLE study the mean total daily ON time without troublesome dyskinesia over 18 hours increased over time for both placebo and treatment groups. At week 24, the mean change from baseline was 0.56 (SE 0.15) hours for the placebo group and 1.52 hours for the (0.15) hours for the safinamide 100 mg/day group. Difference versus placebo was statistical significant i.e. 0.96 hours for the safinamide 100 mg/day group [p < 0.001].

Secondary outcomes Study 016 and SETTLE Study

The OFF time decreased by 0.5 and 1.00 hour in study 016 and the SETTLE study, respectively. There is a statistically significant but slight improvement in UPDRS-III in the ON phase. Dyskinesia score in the ON phase did not improve. Responder rates are in favour of active treatment, although responder rates according to diverse post-hoc definitions (e.g. of >30 minutes improvement of ON-time), were mostly statistically significant.

In Study 016, statistically significant (p=0.006) improvement (-2.2) was observed for the UPDRS II (ON phase) for the safinamide 100 mg/day group compared to placebo (-1.2). The proportion of patients rated as improved on the CGI-C was significantly greater in the safinamide 50 mg/day (66.4%, p=0.001) and 100 mg/day (64.3%, p=0.009) groups, compared to placebo (55.4%). There were no statistically significant differences among the treatment groups in the mean change in Dyskinesia Rating Scale scores during ON phase, H&Y stage, HAMD, MMSE and Cogtest outcomes in study 016. Neither were UPDRSII scores significant for the 50 mg arm.

In the SETTLE study statistically significant improvements in health-related quality of life and functioning, as assessed by the PDQ-39 and EQ-5D scales, were observed. For the UPDRS Section II, DRS and GRID-HAMD, there was no significant difference between groups in the change from baseline in total score.

A post-hoc analysis of "responders", demonstrated that treatment with safinamide 50 mg/day or 100 mg/day was associated with a statistically significantly greater proportion of subjects, compared to placebo, experiencing clinically meaningful benefit, as defined below.

Table 15 Main outcomes Study 016/SETTLE Study

	STUDY 016			SETTLE STUDY	
Study arm	**Placebo** n=222	**50 mg/day** n-223	**100 mg/day** n=224	**50 -100 mg/day** n=274	**Placebo** n=275
ON without troublesome dyskinesia					
Baseline	9.30	9.37	9.52	9.30	9.06
LS mean endpoint	+0.72	+1.23	+1.28	+1.52	+0.56
Difference vs Placebo		0.51	0.55	0.96	
CI95%		0.07 ; 0.94	0.12 ; 0.99	0.56 ; 1.37	
p-value		0.023	0.013	< 0.001	
OFF-TIME (hr)					
Baseline	5.3	5.2	5.2	5.34	5.38
LS Mean Change week 24	-0.7	-1.3	-1.3	-1.65	-0.62
p-value		0.004	0.003		<0.001
UPDRS-III-score (ON)					
Baseline	28.7	27.3	28.3	22.26	23.05
LS Mean Change week 24	-4.3	-6.1	-6.9	-3.52	-1.70
p-value		0.014	0.0006		0.003
Dyskinesia rating (ON)					
Baseline	3.4	3.9	3.7	2.79	2.57
Change week 24	-0.2	-0.3	-0.3	-0.06	-0.29
p-value		0.18	0.24		0.223
UPDRS-II-score (ON)					
Baseline	12.3	11.8	12.1	9.97	10.43
LS Mean Week 24	-1.2	-1.7	-2.2	-1.22	-0.79
p-value		0.125	0.006		0.149
CGI-improvement	55.4%	66.4%	64.3%	57.7%	41.8%
		0.001	0.009		<0.001
CGI-C- much/ very much improvement	19.8%	33.2%	36.1%	24.4%	9.5%
p-value		0.0017	0.0002	<0.0001	
Percentage reduction in l-dopa	-2.12%	-1.41%	-3.21%	-0.97%	-0.91%
		0.14	0.11		0.018
Post hoc responder					

definitions					
≥ 30 minutes improvement on ON	50.5%	61.0%*	63.4%*	-	-
≥ 30 minutes improvement in ON with no increase in dyskinesia and OFF time	40.1%	44.4%	51.8%*	42.3%*	32.7%
≥ 30 minutes improvement in ON AND decrease in OFF time ≥ 30 min and UPDRS III improvement ≥ 30%	19.%	26.5%*	28.6%*	14.6%	9.5%

* statistically significant (the 95% CI of the differences did not contain 0)

Based on these two trials, the Applicant concluded that safinamide at doses of 50 and 100 mg, was able to improve ON time and motor symptoms in mid- to late-stage PD patients on L-dopa therapy, without worsening dyskinesia.

Study 018.

Study 018 concerned a double-blind, placebo-controlled, 18-month extension study of Study 016, where the efficacy and safety of safinamide 50 mg/day and 100 mg/day as add-on therapy to levodopa with or without other anti-Parkinson medication, was further evaluated for another 18 months in patients with motor fluctuations. In total, from baseline of Study 016 on, the study duration was 24 months.

Patients of study 016 willingly to enter study 018 remained in the same treatment group to which they were randomized in originally. The double blind was maintained.

In total 78.8%, 84.8% and 80.3% of the subjects of the subjects who were randomized to placebo, 50 mg/day and 100 mg/day in Study 016, entered study 018. Sixty-four percent, 64.3% and 67.0% of the subjects on placebo, 50 mg-day or 100 mg-day originally randomized in study 016 completed study 018.

The primary efficacy endpoint was the mean change in the Dyskinesia Rating Scale (DRS) during ON time from baseline (Study 016) to the endpoint (last visit in study 018)

For all 3 treatment groups, the median duration of treatment was 2.0 years (016 and 018 combined). The mean days of exposure were 674.4 days (range 166 to 842) for the placebo group, 647.1 days (range, 134 to 814) for the safinamide 50 mg/day group and 679.0 days (range, 147 to 889) for the safinamide 100 mg/day group.

After a total of 24 months, a non-statistically significant mean improvement of –0. 51 and - 0.28 point was observed for safinamide 50 mg / daily dose and 100 mg/day as compared to placebo (see Table 16):

Table 16 Primary endpoint study 018 (ITT-MMRM)

	STUDY 018		
Study arm	**Placebo**	**50 mg/day**	**100 mg/day**
DRS score			
Baseline (016)	3.4	3.9	3.7
Week 12 (016)	-0.2	-0.4	-0.4

Study 018 (baseline) (Week 24 Study 016)	-0.3	-0.2	-0.4
Week 24 (018)	-0.2	-0.5	-0.8
Week 52 (018)	-0.2	-1.0	-0.9
Week 78 (018)	0.0	-1.2	-1.1
Endpoint	0.32	-0.19	-0.28
Difference		-0.51	-0.60
p-value		0.21	0.15

The Applicant argues that the trend for a DRS improvement in both the safinamide groups and the opposite trend i.e. DRS worsening observed for placebo, indicates efficacy.

Post-hoc defined sub-group analyses in 32% of the patients, who presented moderate-to-severe dyskinesia at baseline (i.e. DRS score > 4), revealed a statistically significant difference for the Safinamide 100 mg/day group vs. placebo in the mean change from baseline of DRS score (p= 0.03).

The results for the key secondary measures in study 018 are summarized in the next Table 17.

Table 17 Study 018 summary secondary endpoints

	Treatment Difference vs placebo (95% CI)	
	Safinamide 100 mg/day (n=224)	Safinamide 50 mg/day (n=223)
ON time (ON time + ON time with minor dyskinesia)	0.83 (0.39, 1.27)*	0.67 (0.23, 1.11)*
OFF time, hours	-0.75 (-1.11, -0.38)*	-0.62 (-0.98, -0.25)*
UPDRS part III	-2.13 (-3.65, -0.60)*	-1.05 (-2.58, 0.48)
UPDRS part II	-1.06 (-1.83, -0.29)*	-0.52 (-1.29, 0.25)
UPDRS part IV	-0.68 (-1.04, -0.31)*	-0.12 (-0.49, 0.24)
CGI-S	-0.14 (-0.25, -0.03)*	-0.16 (-0.27, -0.04)*
PDQ-39	-18.36 (-33.75, -2.97)*	-10.48 (-25.94, 4.98)
GRID-HAMD	-0.57 (-1.13, -0.01)*	-0.15 (-0.72, 0.42)
* p < 0.05 Source: 018 CSR EOT Tables: 47.2, 48.2, 55.2, 54.1.2, 56.1.2, 59.2, 64.1.2, 63.1.2		

In conclusion, a significant effect on ON time was maintained at the end of the 24-month extension period for both safinamide doses compared to placebo. For the 50 mg and 100 mg dose groups, p-values were respectively; p=0.0031 and p=0.0002. Hence, after 2 years of treatment, no worsening in ON time with troublesome dyskinesia or minor dyskinesia was observed.

2.7.2.3. Summary of main study(ies)

The following tables (Table 18,
Table 19, Table 20, Table 21, Table 22) summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 18 Summary of Efficacy for trial 015

Trial 015 **Title:** A Phase III, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of a Low (50-100 mg/day) and High (150-200 mg/day) Dose Range of Safinamide, as Add-On Therapy, in Patients with Early Idiopathic Parkinson's Disease Treated with a Stable Dose of a Single Dopamine Agonist.			
Study identifier	NW-1015/015/III/2003		
Design	Randomized, placebo-controlled, double-blind, parallel		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 months not applicable 12 months (blinded, Study 017, see table below)
Hypothesis	Superiority to placebo		
Treatments groups	High dose		150-200 mg safinamide/day, 6 months, n=89
	Low dose		50-100 mg safinamide/day, 6 months, n=90
	Placebo		Placebo, 6 months, n=90
Endpoints and definitions	Primary endpoint	UPDRS-III	Improvement of motor-symptoms scores mean change from baseline, compared to placebo.
	Secondary endpoint	CGI-C responders	Clinical global impression- responders (percentage of subjects with any clinical improvement from baseline (modest-very good)
	Secondary endpoint	UPDRS-III >30% responders	Responder defined as subjects with ≥ 30% improvement from baseline UPDRS-III scores
	Secondary endpoint	UPDRS-II (ADL)	Total scores of the UPDRS-scale ADL section II (Activities of Daily Living) (mean change from baseline)
Database lock	The first patient entered the study on 21 December 2004 and the last patient completed the study on 23 January 2006.		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intention to treat			
Descriptive statistics and estimate variability	Treatment group	High dose (150-200 mg)	Low dose (50-100 mg)	placebo
	Number of subjects ITT	89	90	90
	UPDRS-III (mean change from baseline (SD)	-3.9 (6.01)	-6.0 (7.18)	-3.6 (7.08)
	range	-18; 13	-26; 8	-24; 18
	Secondary endpoints			
	CGI-C responders (%)	59.3%	62.2%	48.9%
	UPDRS >30% improvement responders	36.8%	38.2%	24.7%

	UPDRS-II (ADL) mean change from baseline at Week 24 (SD) range	-1.4 (2.75) -11; 6	-2.2 (3.79) -15; 9	-1.2 (3.52) -18; 6
Effect estimate per comparison	Primary endpoint UPDRS-III LS Diff vs. Placebo	High dose vs Placebo	Low Dose vs Placebo	
		-0.4	-1.9	
		95% CI: [-2.3, 1.4]	95% CI [-3.7, -0.1]	
		p-value= 0.6504	p-value=0.0419	
	Secondary CGI-C responder Diff vs Placebo	High dose vs Placebo	Low Dose vs Placebo	
		10.2 %	13.1 %	
		95% CI [-4.8; 25.2]	95% CI [-1.9; 28.1]	
		p-value= 0.1822	p-value= 0.0829	
	Secondary UPDRS III >30% responder Diff vs Placebo	High dose vs Placebo	Low Dose vs Placebo	
		11.2%#	#12.6%	
		#95% CI : -2.4, 24	#95% CI: -0.9%, 25.5%	
		ns	ns	
	Secondary UPDRS-II (ADL) LS Diff vs. Placebo	High dose vs Placebo	Low Dose vs Placebo	
		-0.5	-0.1	
		95% CI: [-1.3, 0.4]	95% CI [-1.8, -0.1]	
		p-value = 0.2762	p-value= 0.0248	
Notes	# calculated by CHMP.			
Analysis description	**Sensitivity analyses; LOCF imputation**			
	UPDRS-III, difference in mean change from baseline: High dose vs placebo: -0.5 (95% CI (-2.3, 1.2), p-value 0.5425; Low Dose: -1.6 (-3.4, 01), p-value 0.0691)			

Table 19 Summary of Efficacy for the MOTION study

Title: MOTION Study			
Study identifier	27918		
Design	Parallel, randomized, double-blind, add-on, Study population: patients with early Parkinson (without motor fluctuations), on a stable treatment with DA-agonists.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		6 months not applicable A double-blind placebo-controlled extension phase was scheduled, but interrupted by the Sponsor because of inconclusive results of the first phase.
Hypothesis	Superiority to placebo of the High Dose		
Treatments groups	High Dose		100 mg (once daily) for 6 months, Number randomized: 227
	Low Dose		50mg (once daily) for 6 months, Number randomized: 227
	Placebo		placebo (once daily) for 6 months, Number randomized: 225
Endpoints and definitions	Primary endpoint	UPDRS-III	Improvement of motor symptoms (mean change from baseline)
	Secondary	CGI-C -responder	responders defined as subjects with a rating of 1, 2, or 3 on the Clinical Global Impression - Improvement scale (1: , very much improved; 2,: much improved; 3: minimally improved)
	Secondary	UPDRS-III >30%	Responder defined as subjects with ≥ 30% improvement from baseline UPDRS-III scores
	Secondary	UPDRS-II	Total scores of of the UPDRS-scale ADL section II (Activities of Daily Living) (mean change from baseline)
Database lock	Date First Subject Screened—Date Last Subject Completed Last Observation: 27 MAR 2009 – 23 JAN 2012		
Results and Analysis			
Analysis description	**Primary Analysis**		

Analysis population and time point description	Intention to treat Time point: week 24			
Descriptive statistics and estimate variability	Treatment group	100 mg Dose	50 mg Dose	Placebo
	Number of subjects	227	227	225
	Primary endpoint UPDRS-III	Mean change from baseline (SE) −1.98 (0.42)	Mean change from baseline (SE) −1.60 (0.42)	Mean change from baseline (SE) −0.95 (0.42)
Effect estimate per comparison	Primary endpoint UPDRS-III	100 mg versus Placebo	50 mg versus Placebo	
		LS Diff vs. Placebo (SE) −1.04 (0.58)	LS Diff vs. Placebo (SE) −0.65 (0.58)	
		95% CI Diff vs. Placebo: −2.17, 0.10	95% CI Diff vs. Placebo: −1.79, 0.48	
		p-value = 0.073	p-value = 0.259	
	Secondary: CGI-C responders	100 mg versus Placebo	50 mg versus Placebo	
		Diff 5.4% (45.8% vs 40.4% Placebo)	Diff 7.6% (48.0% vs 40.4% Placebo)	
		#95% CI: -3.7, 14.4	#95% CI: -1.6, 16.7	
		ns	ns	
	Secondary: UPDRS III>30% responders	100 mg versus Placebo	50 mg versus Placebo	
		4.3% (24.7% vs 20.4%)	6.5% (26.9% vs 20.4%)	
		#95% CI: -3.5, 11.9	#95% CI: -1.7, 13.2	
		p-value: ns	p-value: ns	
	Secondary: UPDRS-II (ADL)	100 mg versus Placebo	50 mg versus Placebo	
		LS Diff vs. Placebo: −0.45	LS Diff vs. Placebo: −0.38	

		95% CI (−0.96, 0.06)	95% CI (−0.89, 0.13)
		p-value= 0.085	p-value= -0.142
Notes	#calculated by CHMP		
Analysis description	**Sensitivity analyses**		
	MMRM-imputation, primary endpoint UPDRS-III: LS Diff vs. Placebo: −0.80 (95% CI −1.99, 0.39) for the 50 mg dose vs placebo (p-value 0.186); LS Diff vs. Placebo: −0.96 (−2.14, 0.21) for the 100 mg dose vs placebo (p-value 0.109).		

Table 20 Summary of Efficacy for study 017

Title: Study 017			
Study identifier	NW-1015/017/III/2003		
Design	A Phase III, Double-Blind, Placebo-Controlled, 12-Month Extension Study to Investigate the Efficacy and Safety of a Dose Range of Safinamide of 50-200 mg/day as Add-on Therapy in Patients with Early Idiopathic Parkinson's Disease Treated with a Stable Dose of a Single Dopamine Agonist.		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:		12 months 6 months (Study 015) not applicable
Hypothesis	Superiority		
Treatments groups	High Dose		Safinamide 150-200 mg/day, 12 months, n=69 were allocated (from 89 allocated at baseline Study 015)
	Low Dose		Safinamide 50-100 mg/day, 12 months, n=80 were allocated (from 90 allocated at baseline Study 015)
	Placebo		Placebo, 12 months, n=79 were allocated (from 90 allocated at baseline Study 015)
Endpoints and definitions	Primary endpoint	Time to Intervention	'Intervention' is defined as any increment in dopaminergic background therapy (other than Study drug), or Discontinuation due to lack of efficacy

	Secondary	Rate of interventions	Period baseline Study 015-end of Study 017 (18 months)
	secondary	CGI-responde r	responders defined as subjects with a rating of 1, 2, or 3 on the Clinical Global Impression - Improvement scale (1: , very much improved; 2,: much improved; 3: minimally improved)
Database lock	First Patient Enrolled: 13 June 2005 Last Patient Completed: 29 January 2007		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Primary analyses: Intention to treat from baseline Study 015		
Descriptive statistics and estimate variability	Treatment group	Pooled safinamide@	Placebo
	Number of subject	179	90
	time to Intervention (days)	Median: 362	Median: 353.5
	range (days)	2-588	7-563
	Intervention rate	39.7%	47.8%
	CGI-C response#	43.2.%	33.2%
Effect estimate per comparison	Primary endpoint	Pooled safinamide vs Placebo	
		Log rank Median (Time to Intervention) 559.0	Log rank Median (Time to Intervention) 466.0
		p-value=0.3342	
	Intervention rate Difference	Difference versus placebo: 8.1% 95% CI: (-20.4, 4.3)	
	CGI-C response	Difference versus placebo: 10.3% (-3.8, 22)	
Notes	#only data available for the selected subgroup of patients that continued treatment in Study 017		

Table 21 Summary of efficacy for STUDY 016

Title: A Phase 3, Double-Blind, Placebo-Controlled Study to Determine the Efficacy and Safety of a Low (50 mg/day)and High (100 mg/day) Dose of Safinamide, as Add-on Therapy, in Patients with Idiopathic Parkinson's Disease with Motor Fluctuations, Treated with a Stable Dose of Levodopa and Who May be Receiving Concomitant Treatment with Stable Doses of a Dopamine Agonist, and/or an Anticholinergic			
Study identifier	2006-005860-14 NW-1015/016/III/2006		
Design	This study was a Phase 3, multicenter, multinational, double-blind, placebo-controlled, parallel-group study conducted in patients with idiopathic PD with motor fluctuations, who were receiving a stable dose of levodopa. The total duration of the study was approximately 30 weeks, including the Screening period (10 days), a levodopa stabilization phase (4 weeks), the treatment period (24 weeks), and an optional 1-week taper phase. Eligible patients could receive treatment with either safinamide or placebo for a total of 24 weeks. Patients who met the entry criteria at Baseline were randomized (1:1:1) to receive 1 of the 2 doses of safinamide or placebo.		
	Duration of main phase: Duration of Screening period: Duration of levodopa stabilization phase:		24 weeks, and an optional 1-week taper phase 10 days 4 weeks
Hypothesis	Superiority		
Treatments groups	safinamide 50 mg/day (SFNM50)		223 randomized, 181 completed
	safinamide 100 mg/day (SFNM100)		224 randomized, 183 completed
	Placebo (PBO)		222 randomized, 174 completed
Endpoints and definitions	Primary endpoint	mean total daily ON time (mdONt)	mean total *daily ON time* without troublesome dyskinesia over 18 hours
	Secondary endpoint	*daily OFF* time (dOFFT)	decrease in total *daily OFF* time

	Secondary endpoint	UPDRS III	UPDRS Section 3 (motor examination) during on phase	
Analysis description	Primary Analysis			
Analysis population and time point description	ITT population week 24 or LOCF			
Descriptive statistics and estimate variability	**Treatment group**	**PBO**	**SFNM50**	**SFNM100**
	Number of subject	174	181	183
	"mdONt" mean (SD)	10.32 (2.494)	10.88 (2.698)	11.01 (2.685)
	median	10.13	11.00	11.00
	Min, Max	3.0, 17.3	3.0,17.0	3.5,18.0
	Number of subject	214	215	217
	"dOFFT" mean (SD)	4.5 (2.66)	3.9 (2.58)	3.9 (2.48)
	median	4.4	3.3	3.8
	Min, Max	0, 13	0, 13	0, 11
	"UPDRS III" mean (SD)	23.9 (12.60)	21.1 (12.04)	21.3 (12.53)
	median	23.0	19.5	20.0
	Min, Max	2, 65	2, 60	1, 72

Effect estimate per comparison	Primary endpoint **"mdONt"**	Comparison groups	**SFNM50 vs PBO**
		LS difference vs placebo	0.51
		95% CI	(0.07, 0.94)
		P-value	0.0223
	Primary endpoint **"mdONt"**	Comparison groups	**SFNM100 vs PBO**
		LS difference vs placebo	0.55
		95% CI	(0.12, 0.99)
		P-value	0.0130
	Secondary endpoint **"dOFFt"**	Comparison groups	**SFNM50 vs PBO**
		LS difference vs placebo	–0.6
		95% CI	(–0.9, –0.2)
		P-value	0.0043
	Secondary endpoint **"dOFFt"**	Comparison groups	**SFNM100 vs PBO**
		LS difference vs placebo	–0.6
		95% CI	(–1.0, –0.2)
		P-value	0.0034

Table 22 Summary of efficacy for SETTLE trial

Title: A phase III, double-blind, placebo-controlled, randomized trial to determine the efficacy and safety of a dose range of 50 to 100 mg/day of safinamide, as add-on therapy, in subjects with idiopathic Parkinson's disease with motor fluctuations, treated with a stable dose of levodopa and who may be receiving concomitant treatment with stable doses of a dopamine agonist, an anticholinergic and/or amantadine.

Study identifier	2007-002964-90 SETTLE study number: 27919		
Design	This was a double-blind, placebo-controlled, parallel-group, randomized, multicenter, multinational, Phase III trial, comparing a dose range of 50 – 100 mg of safinamide, p.o. q.a.m. versus placebo as add-on therapy to a stable dose of levodopa in idiopathic PD subjects with motor fluctuations. Subjects who met the entry criteria at baseline were randomized (1:1) to receive safinamide (50-100 mg/day) or placebo. The trial consisted of a screening period, followed by a four-week levodopa stabilization phase and a 24-week, double-blind treatment period. The total duration of the trial was approximately 34.5 weeks, including the Screening period (10 days), a levodopa stabilization phase (four weeks), the treatment period (24 weeks), a one-week taper phase, and a safety follow-up phase (four weeks).		
	Duration of main phase:		24 weeks +7 days of taper phase before treatment discontinuation
	Duration of levodopa stabilization phase:		four weeks
	Duration of safety follow-up phase:		four weeks
Hypothesis	Superiority		
Treatments groups	50 – 100 mg of safinamide, p.o. q.a.m (SFNM)		274 randomized patients, 245 (89.4%) completed the study
	Placebo (PBO)		275 randomized patients, 241 (87.6%) completed the study
Endpoints and definitions	Primary endpoint	change in daily *ON time (dONt)*	change in daily *on time* (*ON time* without dyskinesia plus ON time with minor dyskinesia) from baseline to Week 24, as measured by subject diary cards.

	Key secondary endpoint	daily *OFF* time (dOFFt)	daily OFF time, as measured by diary cards, change from baseline to Week 24
	Secondary endpoints	UPDRS Sections II and III	UPDRS Section II and III score during the on phase change from baseline to Week 24;
	Secondary endpoint	Proportion of patients showing improvement	proportion of subjects with scores of 1, 2, or 3 (showing improvement) on the CGI - Change scale at Week 24;
	Secondary endpoint	PDQ-39	PDQ-39 summary index score change from baseline to Week 24
Database lock			
Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	The analysis of the primary endpoint (daily *ON time*) was performed using a LOCF imputation and an ANCOVA model for the ON Treatment population (ITT population with censoring of data post rescue intervention). The population consisted of PD patients with at least 1.5 hours of daily OFF time, disease duration of at least 3 years, minimally 3 daily doses of L-dopa, a Hoehn and Yahr stage of 1-4 during an OFF phase, and the ability to maintain an 18-hour per day diary.		
Descriptive statistics and estimate variability	Treatment group	SFNM	PBO
	Number of subject	n=274	n=275
	PEP "dONt"	Mean 10.73 ±2.75 change 1.42 ±2.80 median 10.75	Mean 9.63 ±2.77 change 0.57 ±2.47 median 9.75

	key SEP "dOFFt"	Mean 3.77 ±2.56 change -1.56 ±2.35 median 3.88	Mean 4.84 ±2.59 change -0.54 ±2.21 median 5.00
	UPDRS III	Mean 18.83 ±10.87 change -3.43 ±7.72 median 17.00	Mean 21.22 ±11.78 change -1.83 ±8.23 median 19.00
	UPDRS II	Mean 8.90 ±5.44 change -1.07 ±3.63 median 9.00	Mean 9.68 ±5.94 change -0.75 ±3.95 median 9.00
Effect estimate per comparison	Primary endpoint "dONt" analysis using ANCOVA [LOCF], ITT Population	Comparison groups	SFNM vs PBO
		LS Diff vs. Placebo (SE)	0.96 (0.21)
		95% CI of LS Diff	0.56, 1.37
		P-value	<0.001
	Primary endpoint "dONt" analysis using MMRM, ITT Population	Comparison groups	SFNM vs PBO
		LS Diff vs. Placebo (SE)	0.93 (0.22)

		95% CI of LS Diff	(0.50, 1.36)
		P-value	<0.001
	Key secondary endpoint (daily *OFF* time)	Comparison groups	SFNM vs PBO
		LS Diff vs. Placebo (SE)	-1.03 (0.19)
		95% CI of LS Diff	(-1.40, -0.67)
		P-value	<0.001

2.7.2.4. Analysis performed across trials (pooled analyses and meta-analysis):

For **early stage PD (ESPD)**, pooled analyses were performed in the mITT population during the procedure. See the Table 23, Table 24 and Table 25 below. Only patients that had used a 50 or 100 mg dose were selected. The differences in dosing schedule (per mg/kg) and the short treatment duration of Study 009 (12 weeks) should not allow for pooling with the other trials (015 and MOTION, both 24 weeks trials). The pooling of MOTION and Study 015 would seem more rational, but still the dosing regimen was different in these two Phase III studies, rendering the value of the pooled data as exploratory only.

Table 23 ESPD Stuties: Summary of Analyses for UPDRS Sections II and III for Pooled Studies (mITT Population)

Study Number(s)	Efficacy Parameter	Statistic p-value (b)	Mean change from baseline to endpoint in UPDRS Sections II, III and II+III					
			MMRM Analysis (c)			ANCOVA-LOCF Analysis (d)		
			50 mg/day	100 mg/day	All Saf	50 mg/day	100 mg/day	All Saf
Pooled 009, 015, MOTION		N	N=280 (a)	N=369 (a)	N=649	N=280 (a)	N=369 (a)	N=649
	UPDRS II	LS Diff vs Pbo	-0.3	-0.5	-0.4	-0.4	-0.7	-0.6
		p-value	0.0809	**0.0011**	**0.0025**	0.0883	**0.0009**	**0.0025**
	UPDRS III	LS Diff vs Pbo	-0.5	-1.2	-0.9	-0.4	-1.6	-1.1
		p-value	0.1458	**0.0003**	**0.0018**	0.3636	**0.0005**	**0.0064**
	UPDRS II + III	LS Diff vs Pbo	-0.8	-1.6	-1.3	-0.8	-2.3	-1.6
		p-value	0.0866	**0.0001**	**0.0006**	0.1949	**0.0002**	**0.0019**
Pooled 015, MOTION		N	N=225	N=314	N=539	N=225	N=314	N=539
	UPDRS II	LS Diff vs Pbo	-0.2	-0.5	-0.4	-0.1	-0.7	-0.5
		p-value	0.2550	**0.0025**	**0.0103**	0.5591	**0.0029**	**0.0243**
	UPDRS III	LS Diff vs Pbo	-0.3	-1.0	-0.7	-0.0	-1.3	-0.8
		p-value	0.3714	**0.0065**	**0.0248**	0.9824	**0.0080**	0.0804
	UPDRS II + III	LS Diff vs Pbo	-0.5	-1.4	-1.1	-0.2	-2.0	-1.2
		p-value	0.2798	**0.0018**	**0.0092**	0.8080	**0.0023**	**0.0342**

ANCOVA=Analysis of Covariance; ESPD=Early-Stage Parkinson's Disease; LOCF=Last Observation Carried Forward; LS Diff vs Pbo=Least Squares Mean Difference vs. Placebo; mITT=modified Intent-to-Treat; MMRM=Mixed Model Repeated Measures; UPDRS=Unified Parkinson's Disease Rating Scale (Section II - Activities of Daily Living; Section III – Motor Examination); All Saf=All safinamide doses combined.

a. Data for doses in Study 009 of 0.5 and 1.0 mg/kg/day have been included under 50 and 100 mg/day, respectively.

b. P-value for comparison between safinamide and placebo; significant effects (p<0.05) are in **bold** text.

c. MMRM model for change from Baseline to Endpoint includes treatment, region, and visit as fixed effects, and baseline value as a covariate.

d. ANCOVA model is based on change from Baseline to Endpoint with fixed effects for treatment, study, and baseline value as a covariate.

Source: Response to 120-Day Assessment, Answer to Question 59A, Tables 59-17 and 59-20.

Table 24 ESPD Studies Summary of Responder Analyses for pooled Studies (mITT Population)

Study Number(s)	Responder Definition	Statistic p-value (b)	Treatment Group			
			50 mg/day	100 mg/day	All Saf	Placebo
Pooled 009, 015, MOTION		N	N=280 (a)	N=369 (a)	N=649	N=369
	≥30% improvement in UPDRS III	% Responders	27.9	30.92	29.6	23.6
		p-value	**0.0303**	**0.0225**	**0.0100**	----
	≥40% improvement in UPDRS III	% Responders	18.9	22.2	20.8	13.6
		p-value	**0.0048**	**0.0018**	**0.0007**	----
	≥50% improvement in UPDRS III	% Responders	11.4	14.4	13.1	7.6
		p-value	**0.0269**	**0.0033**	**0.0028**	----
	≥20% improvement in UPDRS II + III	% Responders	39.3	42.8	41.3	32.8
		p-value	**0.0047**	**0.0042**	**0.0010**	----
	≥30% improvement in UPDRS II + III	% Responders	25.4	29.3	27.6	20.1
		p-value	**0.0046**	**0.0031**	**0.0009**	----
Pooled 015, MOTION		N	N=225	N=314	N=539	N=313
	≥30% improvement in UPDRS III	% Responders	27.1	29.6	28.6	24.0
		p-value	0.0526	0.0990	**0.0411**	----
	≥40% improvement in UPDRS III	% Responders	17.8	20.7	19.5	13.7
		p-value	**0.0125**	**0.0180**	**0.0058**	----
	≥50% improvement in UPDRS III	% Responders	10.7	13.1	12.1	7.3
		p-value	**0.0349**	**0.0177**	**0.0102**	----
	≥20% improvement in UPDRS II + III	% Responders	36.9	42.8	40.1	32.6
		p-value	**0.0192**	**0.0099**	**0.0040**	----
	≥30% improvement in UPDRS II + III	% Responders	24.0	29.3	27.1	20.4
		p-value	**0.0180**	**0.0086**	**0.0037**	----

Table 25 Pooled ESPD Studies 009, 015, 27918 (MOTION): Responder Analyses for Clinical Global Impression of Change (CGI-C) (mITT and Completer Populations)

Pooled ESPD Studies 009, 015, 27918 (MOTION): Responder Analyses for CGI-C (Change from Baseline to Endpoint)									
Responder Definition	Statistic p-value (a)	mITT Population				Completer Population			
		50 mg/day (n=280)	100 mg/day (n=369)	All Saf (n=649)	Placebo (n=369)	50 mg/day (n=249)	100 mg/day (n=336)	All Saf (n=585)	Placebo (n=327)
CGI-C - any improvement (b)	% Responders	45.4	48.2	47.0	39.6	48.6	51.8	50.4	42.5
	p-value	**0.0176**	**0.0157**	**0.0053**	----	**0.0147**	**0.0136**	**0.0043**	----
Much/Very Much Improvement in CGI-C (c)	% Responders	14.3	18.4	16.6	12.7	15.3	20.2	18.1	13.5
	p-value	0.0646	**0.0289**	**0.0185**	----	0.0574	**0.0152**	**0.0110**	----

CGI-C=Clinical Global Impression – Change from Baseline; mITT=modified Intent-to-Treat; Saf=Safinamide; All Saf=safinamide 50 mg/day and 100 mg/day combined.

a. P-values are based on chi-square tests of the odds ratio of each treatment group (50 mg/day, 100 mg/day, and All Safinamide) compared to placebo using a logistic regression model, with fixed effects for treatment and country, significant effects ($p<0.05$) are in **bold** text.

b. Improvement = a value of 1, 2, or 3

c. Much/Very Much Improvement = a value of 1 or 2

For **late stage PD (LSPD),** i.e. patients on levodopa with motor fluctuations, additional analyses were performed to compare the proportion of LSPD patients in the safinamide 50 and 100 mg/day dose groups vs. placebo that exhibit a clinically meaningful response to treatment. Clinically meaningful effects were defined using a series of responders definitions based on categorical changes from baseline to endpoint for ON time, OFF time, UPDRS III, PDQ-39, as well as the rating of change from baseline at endpoint on the CGI-Change (CGI-C). The responder analyses evaluated safinamide doses of 50 and 100 mg/day separately.

Logistic regression analyses comparing proportions of responders were performed on the mITT population using data pooled from studies 016 and SETTLE. P-values from the analyses were based on Chi-square tests of the odds ratios of each safinamide treatment group compared to placebo, using a logistic regression model, with fixed effects of treatment and study.

The results of these analyses are summarized below in Table 26:

Table 26 Responder Rates by Treatment Group - Late Stage PD - mITT Population

		Safinamide		Placebo
		50 mg/day	100 mg/day	
		(N=236)	(N=467)	(N=485)
Parameter	Responder Variables	Responder n(%)	Responder n(%)	Responder n(%)
ON time	Increase ≥30 min from Baseline to Endpoint	146 (61.9)	305 (65.3)**	261 (53.8)
	Increase ≥60 min from Baseline to Endpoint	124 (52.5)	268 (57.4)**	210 (43.3)
OFF time	Decrease ≥30 min from Baseline to Endpoint	157 (66.5)	313 (67.0)**	285 (58.8)
	Decrease ≥60 min from Baseline to Endpoint	136 (57.6)*	272 (58.2)**	225 (46.4)
UPDRS III	Improvement ≥30%	87 (36.9)	174 (37.3)**	131 (27.0)
Combined	Increase in ON ≥30 min, decrease in OFF ≥30 min, and no worsening of dyskinesia	108 (45.8)	200 (42.8)**	168 (34.6)
	Increase in ON ≥30 min, decrease in OFF ≥30 min, and any improvement on PDQ-39	86 (36.4)	182 (39.0)**	137 (28.2)
	Increase in ON ≥30 min, decrease in OFF ≥30 min, and UPDRS III improvement ≥30%	59 (25.0)	116 (24.8)**	74 (15.3)
	Increase in ON ≥60 min, decrease in OFF ≥60 min, and UPDRS III improvement ≥30%	51 (21.6)*	103 (22.1)**	56 (11.5)
CGI	Any Improvement in CGI-Change from Baseline Rating	152 (64.4)	298 (63.8)**	238 (49.1)
	Any Improvement in CGI-Severity Rating	92 (39.0)*	153 (32.8)*	123 (25.4)

p-value: * p <0.05; ** p <0.01; *Source:* Table RESPL2.1 LATE PD

The safinamide 100 mg/day dose showed a consistent pattern of statistically significant improvement compared to placebo, regarding categorical response in ON and/or OFF time, dyskinesia, PDQ-39 or UPDRS III and clinical global assessments performed by the physician (CGI-C). Although the proportions of responders in the 50 mg/day dose group were similar to those for the 100 mg/day dose, no statistical significance was achieved for the majority of the secondary endpoints. This lack of significance might be related to the lower number of patients in the 50 mg/day dose (n=236) compared with the 100 mg/day dose (n=467)). Moreover, the majority of patients in the 50 mg/day group came from Study 016, where the change from baseline was much smaller.

2.7.2.5. Supportive study(ies)

Study 024 was a Phase II randomised, placebo-controlled exploratory multi-centre trial on the effect of safinamide 100 mg/day on cognitive functioning in 103 Parkinson patients with mild cognitive impairment on a stable treatment with other dopaminergic medicines. Mean Montreal Cognitive Assessment Total Score was 22.6 (SD 2.79) at baseline, indicating mild impairment (a final total score of 26 and above is considered normal). The primary efficacy parameter was the change from Baseline to Endpoint (Week 12 or early discontinuation) in the total score for the Parkinson's Disease Cognitive Rating Scale (PD-CRS). The mean improvement from Baseline to Endpoint was similar between the two treatment groups. At Endpoint, the safinamide group had a mean (SD) change of 2.1 (7.37), and the placebo group of 2.4 (7.64). The LS mean (SE) difference between the safinamide and placebo groups was -0.20 (1.547); this difference was not statistically significant (p=0.8969). Secondary endpoints of mood, sleep, and behaviour (including apathy) did not show an effect.

Although there are some shortcomings in this study, e.g. its short duration and the fact that patients were only mildly cognitively impaired leaving little room for improvement, it could be concluded that

safinamide has no significant impact on cognitive functioning in the short term. This was also further confirmed in the main trials, where safinamide did not significantly change the scores of a cognition test battery in the longer term follow-up (6 months).

2.7.3. Discussion on clinical efficacy

2.7.3.1. Early Parkinson Disease

2.7.3.1.1. Design and conduct of clinical studies, efficacy data and additional analyses

In support of the sought indication of "add-on therapy to a single DA-agonist at a stable dose in early stage non-fluctuating patients", results of three randomised, parallel, double-blind, placebo-controlled studies were provided: Study 009, Study 015 and the MOTION study. In addition, Study 017, a long term extension study of Study 015 was provided, wherein the blind and placebo-control was maintained till 18 months.

In **Study 009**, both treatment naïve patients and patients on treatment with DA-agonist were equally randomised to either safinamide 0.5 mg/kg, 1 mg/kg or placebo. Primary endpoint was ≥ 30% improvement in the UPDRS III motor symptoms at 12 weeks. Although the results from study 009 indicated an effect for the 1 mg/kg dose (responder rate was significantly better than placebo – 37.5% vs 21.4%), this was not considered as sufficient evidence to support the sought after indication. The study was small and its duration of 3 months was too short to provide robust evidence of efficacy on its own.

In Study 015, 269 patients on stable level of DA-agonists without motor fluctuations, were randomised to either low dose safinamide (50-100 mg), high dose safinamide (150-200mg) or placebo in a 1:1:1 ratio. Primary outcome for study 015 was the change in UPDRS-III motor score at week 24 as compared to baseline. Formally, study 015 did not meet its primary objectives, as hypotheses testing should have been stopped, according to the pre-specified hierarchical testing schedule, because of the non-significant results for the 150-200 mg dose group (-3.9 vs -3.6 for placebo, p=0.06504). Thus, the results of this study remained inconclusive even if the difference in the lower dose group came out to be statistically significant.

In addition to the methodological limitations, the effect size observed was small and was not considered to be of clinical relevance. The postulated effect size in the sample size calculations i.e. a difference of -3.3 points is generally perceived as clinically relevant. This value is much larger than the observed difference of -1.9 points for the lower dose group. Moreover this difference did not translate into a beneficial effect in terms of UPDRS-III responder rates and CGI responders' rates, two secondary endpoints that are commonly used to assess clinical relevance of an effect on the primary endpoint in Parkinson's Disease.

Overall, based on the study 015 results, conclusions on the efficacy of safinamide as add-on to dopamine-agonist monotherapy in early Parkinson disease could not be drawn as the methodological soundness and the clinical relevance were questioned.

The **MOTION** study was a randomised double-blind placebo controlled study in 679 patients with early Parkinson's Disease on dopamine-agonist monotherapy. Primary endpoint was the mean improvement from baseline UPDRS-III score. The MOTION study was an important study considering that it was large and included a substantial number of EU participants (45%).

The observed differences versus placebo (UPDRS III Score difference safinamide 50/100 mg -1.6 and -1.9, placebo -0.95, P= 0.27 and P=0.07 respectively) were not statistically significant for the primary endpoint and for the responder results. A small, but statistically significant effect (-2.09, P=0.04) in the primary endpoint was achieved in post-hoc analyses excluding subjects who used two DA-agonists at

baseline, but the inclusion of subjects on two DA-agonists raised additional concerns about the study conduct as these subjects should not have been enrolled based on the inclusion criteria.

In conclusion, the MOTION study appeared to provide similar results to those from study 015 and the clinical relevance of the observed effects was questioned for the same reason as put forward for study 015.

In the double-blind extension **Study 017**, subjects from Study 015 could continue their originally allocated study medication for another 12 months. The study was kept blind. Primary outcome was time to intervention defined by a change in treatment i.e. either an increase in dose of the background DA-agonist or addition of further concomitant anti-Parkinson medication.

The results of study 017 were considered inconclusive by the CHMP since the low event rate and the prolonged median time to intervention of more than one-year questioned the sensitivity for change in this population. The results suggested that the Parkinson's disease population that had been included were early stage well-controlled patients. However, whether this good control was achieved due to the dopamine-agonist used, due to the addition of safinamide, or due to the patients being in a mild stage of the disease with slow progression of symptoms, was impossible to determine.

Considering the results from the pivotal trials, it was difficult to draw a conclusion regarding the optimal dose as no clear dose-response relationship could be established. The company did not investigate the reasons for the lack of dose effect relationship, which apparently was present in study 009. Some effect was observed in the 100 mg-day dose group (Study 015, MOTION study), but neither the 50 mg (MOTION study) nor the 200 mg /day (Study 015) where convincingly shown to be effective.

During the assessment the applicant provided a standardised analysis for all individual studies in EPSD as well as pooled analyses of the studies. A more consistent treatment effect on the UPDRSR-III, in terms of statistical significance, was seen for the 100 mg/day in the combined analysis (studies 009/15/M0TION or 015/MOTION – UPDRS III difference vs PBO was -1.2; P= 0.0003). However, the pooling of studies 009/015/MOTION was considered inappropriate as the doses and dosing regimens used, as well as the duration of treatment, were different.

In addition to the methodological limitations, in the MMRM analyses in the newly defined mITT populations, a significant effect was shown for UPDRS III at the 100 mg dose in all 3 studies (Study 009 (n=33 included); change from baseline (p-values, CI not reported): -2.3 (p=0.0182), Study 015 (n=87 included): -0.9 (p=0.0442), MOTION trial (n=227): -0.3 (p=0.0374). No significant effect was shown for the 50 mg dose in these post-hoc analyses. These outcomes are considerable smaller than what was defined *a priori* as a clinical relevant response of UPDRS III motor scores in the protocol (MOTION: 2.7, Study 015: -3.3). The observed changes in UPDRS III motor scores were not consistently supported by a significant improvement in daily functioning (UPDRS II ADL scores), illustrating that the clinical relevance of the change in motor scores was questionable.

The increased statistical significance shown in the presented pooled data analysis did not address the issue about the clinical relevance of the results. The observed effect sizes were considered small. In the pooled analysis of the two pivotal studies in ESPD (015 & MOTION) the improvement in the UPDRS-III score was 2.0 points for the placebo group (baseline 20.1 points) and 3.0 points for the safinamide 100 mg/day group (difference 1.0 CI 95% -1.6 ; -0.3, p=0.007). The applicant argued that for an add-on treatment to a dopamine-agonist, in this patient population, showing a greater effect size would be a high hurdle. Indeed it was recognized that there could be several arguments to expect less efficacy gains in this population, the question remained though, whether the observed additional effect was still clinically relevant and worth achieving. In both studies (study 015, MOTION) the predefined effect size, indicated as relevant in the power analysis, was not met. The results of the various responder analyses, including

CGI-C responders were not consistent. Differences in responder rates were rather small and never exceeded the 10%. Moreover within CGI-responders the percentage of subjects that improved much/very much was rather low with a difference in responder rate of 5%.

In summary the promising results of the phase II study 009 could not be replicated in the broader Parkinson Disease population receiving dopamine agonists and both pivotal studies performed in early stage PD patients were considered as failed. This was because the methodological issues in the way the primary analysis results were achieved and because the clinical relevance of the additional observed effect of safinamide on top of dopamine–agonist treatment remained questionable. The pooled data analysis improved the statistical significance of the results but did not address the clinical relevance issue. Additionally, the principles according to which the pooled analysis was performed were questioned from a methodological point of view.

2.7.3.2. Late stage Parkinson Disease indication, Add-on to L-dopa

2.7.3.2.1. Design and conduct of clinical studies, Efficacy data and additional analyses

In support of the sought indication of "as add-on to L-dopa, alone or in combination with other PD medication, in mid- to late-stage PD patients with motor fluctuations", data of two 24-week, randomised, parallel, double blind, placebo-controlled studies were provided, i.e. Study 016 and the SETTLE study. Patients with Parkinson's disease with motor fluctuations despite treatment with L-dopa -with or without other PD treatments, like anticholinergics, amantadine, DA-agonists or COMT inhibitors were eligible. Both studies lacked an active comparator. The primary endpoint was change in daily ON time without troublesome dyskinesias at 24 weeks, as recorded in the patient's diary.

The main difference between the pivotal trials in support of the late stage PD indication was that in Study 016 and 018 there were two fixed dose arms (safinamide 50 mg/day, safinamide 100 mg/day) whereas in the SETTLE there was a flexible dose range 50-100 mg/day. However the majority of subjects in the SETLLE Study received and maintained the 100 mg daily dose. Another difference is that Study 016 was predominantly conducted in India (80%), whereas the SETTLE study was global.

In addition, Study 018, the long-term extension study of study 016 was performed, wherein the blinding and placebo-control was maintained for another 18 months till a total duration of 24 months.

Total number of subjects was 669 and 549 for Study 016 and the SETTLE Study, respectively. The measured baseline ON time ranged from 9.06 to 9.52 hours over the study arms.

In study **016,** the mean change from baseline to Week 24 of the ON-time without troublesome dyskinesias (primary endpoint) was 0.72, 1.23 and 1.28 hour for placebo, safinamide 50 mg and 100 mg, respectively. Differences versus placebo were 0.51 (CI95% 0.07; 0.9, p=0.0223) and 0.55 hours (CI95% 0.12; 0.99, p=0.013) for the 50 mg and 100 mg safinamide dose, respectively.

In the **SETTLE** study, ON time without troublesome dyskinesias at Week 24 improved by 0.56 and 1.52 hours for placebo and safinamide 50-100 mg/dose group, respectively. Difference versus placebo was 0.96 hrs (CI95% 0.56; 1.37; p <0.001).

For both studies the observed effects in ON time were reflected in a reciprocal decrease in OFF-time.

In general, the effects on secondary endpoints were consistent with the main results. Several post-hoc defined responders rates, e.g. 30 minutes improvement in ON time (without increase in dyskinesia) and OFF time were in favour of the 100 mg dose groups (i.e. 40.1 % for Placebo versus and 51.8% in safinamide 100mg group in Study 016, whereas no significant difference was achieved for the 50 mg dose group.

Dyskinesia score in ON did not improve, which is expected as ON and dyskinesias are related. It may be argued that dyskinesia would have been expected to worsen if the dopaminergic tone increases.

As no active comparator was included, the magnitude of the observed treatment effects is difficult to appreciate. One of the factors providing reassurance on the relevance were the results of the responder analyses in late stage PD patients. Moreover efficacy of safinamide was favourable in the comparison to historical data of other treatments such as pramipexole or rasagiline. The improvements of 0.51h or 1h in ON time, respectively, were deemed clinically relevant in this population of advanced patients with motor-fluctuations, however the claims with respect to a beneficial effect on dyskinesias could not be substantiated by data. Another point of discussion was the heterogeneity of the outcomes between the two pivotal studies in late stage PD patients. The differences in point estimates between the pivotal studies (016/ SETTLE) fell within the variability seen in studies with other treatment options, and were considered as probably due to differences in the study populations.

Study 018 was the 18-month extension phase of Study 016. Patients of study 016 willing to enter study 018 remained in the same treatment group which they were randomized in originally and the blinding was maintained. From the 667 patients of Study 016, 544 continued their allocated study treatment in Study 018. The median duration of treatment was 2.0 years from baseline of Study 016.

For the primary endpoint i.e. mean change in dyskinesia score during ON-time, a worsening of 0.32 points was observed in the placebo group (baseline 3.4 points). For the safinamide 50 mg group an improvement of 0.19 points (baseline 3.9) was observed. For safinamide 100 mg/day a 0.28 points improvement (from baseline 3.7 points) was observed. These differences were not statistically significant. The applicant argued that the observed trend in dyskinesia score, i.e. an improvement in the 50 and 100 mg/d arms versus a worsening in the placebo arm, was indicative for efficacy, but to make such a claim it was considered that further confirmatory data would be needed.

Overall, the L-dopa dose increased by 18%, 10% and 5 % in the placebo, 50 mg and 100mg/day group, respectively, which further illustrated maintenance of efficacy regarding the effect on improvement of motor symptoms.

2.7.4. Conclusions on the clinical efficacy

2.7.4.1. Early Parkinson Disease add-on to dopamine-agonists

Efficacy of safinamide in the treatment of early Parkinson's disease in an add-on setting to DA-agonists was considered as not established.

Both pivotal studies performed in early stage PD patients were considered failed as the primary analysis results were not statistically significant, and the clinical relevance of the additional effect of safinamide given on top of dopamine–agonist treatment remained questionable. The pooled data analysis improved the statistical significance but did not address the clinical relevance issue. The data in early stage PD patients was not sufficient both from methodological and clinical points of view.

2.7.4.2. Late stage Parkinson Disease Add-on to L-dopa

A statistically significant and clinically relevant effect of safinamide was demonstrated in the add-on setting to L-dopa, and other PD medication in late stage patients. For both studies providing the data in support of this indication the differences in the observed treatment effects were statistically significant, and a dose response relationship was shown. The change in concomitant anti-Parkinson medication was not large and was considered unlikely to be affecting the results. The clinical relevance of the effect could be concluded from the results of the responder analyses in late stage PD patients, and from the more

favourable effect shown in the indirect comparison to other treatments used in this setting.

2.8. Clinical safety

The analysis of the safety of Safinamide is based on the results of 37 trials, comprising 20 phase I trials, 9 phase II trials, and 8 phase III trials. All data collected to date are included in the analysis of safety. There were no ongoing trials at the time of MAA.

The dossier included two patient population i.e. patients with early stage Parkinson's disease (ESPD) on a single dopamine agonist and patients with mid/late stage Parkinson's disease (LSPD) using a stable dose of L-dopa, alone or in combination with other medications for Parkinson's disease.

2.8.1. Patient exposure

The safety population data consisted of analyses sets i.e. group 1: Subjects in the double-blind, placebo-controlled phase II and III trials (pooling of controlled trials with ESPD and LSPD patients) and Group 2: Open-label trials: treatment results of study 28850 which concerned a long term safety extension study of Safinamide in ESPD and LSPD(n=964).

The number of patient exposed and duration of exposure is presented below (Table 27). In total, 3169 study subjects participated in the clinical development program of Safinamide.

Table 27 Subject exposure to Safinamide, placebo or comparator

Investigational arm	**Safinamide**	**Placebo#**	**Overall number of subjects##**
Patients with Parkinson's disease in placebo-controlled studies and open label extension studies (pooled data)			
ESPD	795	422	1217
LSPD on Levodopa	721	497	1218
Patients with Parkinson's disease that took Safinamide for the first time in the Open label extension study	400**		
Total	**1916**	**919**	**2435**
PD patients in other studies (not pooled)			
Other therapeutic studies	69	6	75
Non therapeutic studies	28	22	29
Total	**97**	**28**	**104**
Total number of patients with Parkinson's disease	**2013**	**947**	**2539**

Other studies in subjects without Parkinson's disease			
Therapeutic studies	56	2	58
Non therapeutic studies	399	210	572
Total	**455**	**212**	**630**
OVERALL TOTAL	**2468**	**1159**	**3169**

#placebo and/or active comparator

400 patients in the open label extension phase (previously on placebo) and 58 enrolled in the cross-over study are counted only once in the overall Safinamide program

About half of the ESPD patients (49%) were exposed to Safinamide for more than one year. None of the ESPD patients was exposed to this treatment for more than three years. 71% Of LSPD patients were exposed to Safinamide for more than one year, 16% (n= 169) patients for more than four years (Table 28):

Table 28 Number of patients receiving safinamide in the clinical trials by duration of exposure in clinical trials

	Any	> 6 months	>1 year	>2 years	> 3 years	> 4 years
ESPD patients	879 (100%)	542 (62%)	428 (49%)	110 (13%)	0	0
LSPD patients	1036 (100%)	876 (85%)	734 (71%)	414 (40%)	222 (21%)	169 (16%)
Total	**1949**	**1440**	**1180**	**533**	**222**	**169**

The mean (SD) duration of Safinamide treatment was 56 (36) weeks for Group 1 ESPD patients and 59 (40) for LSPD patients of this Group. The mean (SD) duration of placebo treatment was in Group 1 was 50 (36) weeks for ESPD patients and 48 (38) weeks for LSPD patients. Mean (SD) treatment duration for patients from Group 2 was 108 (72) weeks (Table 29):

Table 29 Duration of exposure in pooled dataset

	ESPD		**LSPD**		**Open label ESPD + LSPD**
	Safinamide	**Placebo**	**Safinamide**	**Placebo**	

Number of patients	795	422	721	497	1025
Mean (SD) treatment duration, weeks	55.7 (36.06)	49.8 (35.99)	59.1 (40.24)	48.3 (37.95)	108.0 (72.24)
Median treatment duration, weeks	64.0	39.3	30.4	25.1	98.1

2.8.2. Adverse events

Treatment-Emergent Adverse Events (TEAEs) for placebo-controlled trials (Group 1) and open label trials (Group 2) are summarised by organ system below. Adverse event of specific interest are presented thereafter.

Late stage PD patients in group 1 experienced more overall adverse events (AEs) than early stage PD patients in Group 1 and patients of Group 2 i.e. 82.4% vs. 70.3% and 73.1% respectively. The occurrence rates of adverse events were in general similar for safinamide doses for ESPD patients. In LSPD patients, adverse events tended to occur more often for dosages of 50 mg safinamide per day (88.5%) compared to 100 mg safinamide per day (79.3%).

Serious adverse events occurred in 6.9% of ESPD patients on safinamide treatment and in 5.0% of these patients on placebo treatment. For LSPD patients, these rates were 12.9% and 11.5% respectively. In ESPD patients, withdrawal due to side effects was 3.9% for a dosage of 50mg safinamide/day, 5.4% for 100mg safinamide/day and 6.7% for 150-200mg safinamide/day. For LSPD patients these rates were 9.1% for 50mg safinamide/day and 6.1% for 100mg safinamide/day. Mortality was <1% for ESPD patients. The mortality in LSPD patients who received 50mg and 100mg safinamide per day was 2.5% and 1.5% respectively.

Table 30 Summary of TEAEs for safinamide

	Placebo-controlled studies (Group 1)								Open label studies (Group 2)
	ESPD					LSPD			
	Safinamide (mg/day)			Placebo		Safinamide (mg/day)		Placebo	
	50	100	150-200*			50	100		
Number of patients	282	424	89	422		243	478	497	1025
Any adverse event	68.4%	72.4%	66.3%	73.0%		88.5%	79.3%	78.3%	73.1%
Any serious adverse event	7.1%	6.6%	7.9%	5.0%		14.0%	12.3%	11.5%	14.9%
Withdrawal due to adverse events	3.9%	5.4%	6.7%	6.6%		9.1%	6.1%	5.4%	4.0%
Death	0.4%	0.5%	1.1%	0.2%		2.1%	2.7%	2.0%	2.7%
Adverse events									
Nervous system disorders	27.3%	28.5%	32.6%	30.1%		59.7%	42.3%	37.8%	30.4%
Gastro-intestinal disorders	21.6%	24.8%	29.2%	25.1%		26.7%	26.4%	21.5%	20.5%
Infections and infestations	28.7%	21.9%	19.1%	22.0%		18.5%	22.4%	17.9%	21.3%
Influenza	4.3%	3.3%	2.2%	2.6%		0.4%	0.8%	0.2%	0.8%
Musculoskeletal and connective tissue disorders	24.1%	20.5%	19.1%	22.7%		30.0%	20.3%	21.1%	21.1%
Myalgia	0	1.2%	2.2%	1.9%		1.6%	0.8%	1.4%	1.1%
Skin and subcutaneous tissue disorders	11.7%	8.0%	4.5%	8.5%		11.5%	11.5%	9.9%	9.9%
Melanoma	0	0	0	0		0	0	0	<0.1%
Eye disorders	13.1%	16.0%	19.1%	14.5%		27.2%	15.9%	18.5%	10.9%
Psychiatric disorders	16.7%	13.7%	14.6%	15.4%		19.8%	15.9%	15.3%	17.1%
General disorders and administration site conditions	14.2%	13.2%	16.9%	17.3%		29.6%	19.5%	19.7%	15.2%

	Placebo-controlled studies (Group 1)								Open label studies (Group 2)
	ESPD					LSPD			
	Safinamide (mg/day)			Placebo		Safinamide (mg/day)		Placebo	
	50	100	150-200*			50	100		
Number of patients	282	424	89	422		243	478	497	1025
Any adverse event	68.4%	72.4%	66.3%	73.0%		88.5%	79.3%	78.3%	73.1%
Pyrexia	1.8%	2.1%	6.7%	3.3%		9.5%	4%	4.8%	3.4%
Investigations	13.5%	13.9%	12.4%	13.0%		31.3%	18.8%	22.3%	12.1%
Injury, poisoning, and procedural complications	12.1%	9.2%	4.5%	8.1%		13.2%	11.7%	9.7%	11.9%
Respiratory, thoracic and mediastinal disorders	8.5%	7.1%	12.4%	8.1%		9.9%	7.5%	6.8%	6.7%
Vascular disorders	6.4%	7.8%	13.5%	8.3%		12.3%	9.0%	8.2%	6.0%
Cardiac disorders	6.4%	3.1%	6.7%	4.7%		4.9%	4.2%	4.4%	4.9%
Metabolism and nutrition disorders	4.6%	8.0%	7.9%	5.9%		15.2%	8.6%	9.5%	-
Renal and urinary disorders	6.7%	3.3%	9.0%	4.3%		12.8%	5.9%	8.9%	5.6%
Ear and labyrinth disorders	4.6%	4.0%	2.2%	2.8%		2.9%	2.7%	1.8%	-

***** 82 Of 89 patients (92%) received 200mg of safinamide

Adverse events of special interest:

2.8.2.1. Nervous system disorders

Approximately 30% of Group 1 ESPD patients and patients in open label studies experienced nervous system disorders, compared to 40-50% of Group 1 LSPD patients. With respect to ESPD patients, the occurrence of adverse events tended to increase with the dose (27.3% for 50mg safinamide; 32.6% for 150-200mg safinamide), while a reverse effect has been observed for LSPD patients (59.7% for 50mg safinamide; 42.3% for 100mg safinamide).

The most frequently (≥5%) observed AEs in ESPD patients were dizziness, headache, and somnolence. For LSPD patients, dyskinesias, headache, and tremor were observed most frequently. The occurrence of dyskinesias and headache tended to decrease with increasing safinamide dose. The occurrence of dyskinesias was much lower for ESPD patients (0-0.2%) compared to LSPD patients (12.9-31.3%).

Table 31 Nervous system TEAEs for Safinamide

	Placebo-controlled studies (Group 1)								**Open label studies (Group 2)**
	ESPD					**LSPD**			
	Safinamide (mg/day)			**Placebo**		**Safinamide (mg/day)**		**Placebo**	
	50	100	150-200 *			50	100		
Number of patients	282	424	89	422		243	478	497	1025
Nervous system disorders	27.3%	28.5%	32.6%	30.1%		59.7%	42.3%	37.8%	30.4%
Dyskinesia	0	0.2%	0	0.2%		31.3%	20.7%	12.9%	10.4%
Dizziness	8.5%	6.4%	6.7%	6.9%		3.7%	2.9%	3.6%	3.9%
Headache	6.0%	8.0%	6.7%	7.3%		8.6%	6.7%	6.2%	3.6%
Somnolence	7.8%	5.0%	5.6%	7.1%		3.3%	4.4%	4.0%	1.6%
Tremor	4.3%	2.1%	3.4%	3.6%		5.8%	1.5%	3.6%	1.6%
Paraesthesia	2.5%	2.4%	0	1.7%		1.6%	1.9%	1.0%	1.2%
Hypoaesthesia	1.1%	1.4%	0	0.9%		0.8%	2.9%	0.6%	0.9%
Memory impairment	0.4%	0.7%	0	0.5%		1.2%	0.6%	0.6%	0.7%
Dystonia	0.4%	0.5%	0	0.5%		3.3%	0.6%	1.0%	0.5%
Convulsion	0.4%	0	0	0		0%	0	0.2%	0.3%

***** 82 Of 89 patients (92%) received 200mg of Safinamide

Adverse events with an occurrence rate of ≥5% have been underlined

The severity of dyskinesias was mild to moderate in most patients. Approximately 4% of ESPD patients had a fall incident, compared to 6-8% of LSPD patients. Less than 2% of falls resulted into a fracture.

Table 32 Dyskinesias by severity for Safinamide

	Placebo-controlled studies (Group 1)				Open label studies (Group 2)
	ESPD		LSPD		
	Safinamide	Placebo	Safinamide	Placebo	
Number of patients	795	422	721	497	1025
Dyskinesia	0.1%	0.2%	24.3%	12.9%	10.4%
Mild	0.1%	0.2%	11.8%	6.4%	5.7%
Moderate	0	0	10.5%	4.6%	4.3%
Severe	0	0	1.9%	1.8%	0.5%
Fall	3.7%	4.0%	8.3%	6.0%	6.0%
Subjects with only a fall (at least one) and no fracture events	3.3%	3.8%	6.9%	5.0%	5.1%
Subjects with both a fall and fracture event (at least one event)	0.4%	0.2%	1.4%	1.0%	1.0%

2.8.2.2. Psychiatric symptoms

15-20% of ESPD and LSPD patients experienced psychiatric adverse events. The general occurrence rates for both ESPD and LSPD patients tended to decrease with increasing safinamide dose.

Except for insomnia and anxiety, other psychiatric adverse events occurred in less than 5% of patients. The most frequently observed psychiatric symptoms were hallucinations, insomnia, depression, and anxiety. Impulse-control disorders, obsessive thoughts, compulsions and increased libido were hardly found in the Safinamide development program (< 0.5%).

Table 33 Summary of psychiatric TEAEs for Safinamide

	Placebo-controlled studies (Group 1)								**Open label studies (Group 2)**
	ESPD					**LSPD**			
	Safinamide (mg/day)			**Placebo**		**Safinamide (mg/day)**		**Placebo**	
	50	100	150-200 *			50	100		
Number of patients	282	424	89	422		243	478	497	1025
Psychiatric disorders	16.7%	13.7%	14.6%	15.4%		19.8%	15.9%	15.3%	17.1%
Hallucination	1.6%	0.5%	1.1%	1.3%		2.9%	2.9%	3.2%	3.4%
Insomnia	5.0%	4.1%	3.4%	6.1%		8.6%	5.2%	4.0%	3.2%
Depression	3.9%	1.8%	2.2%	3.8%		2.5%	2.5%	4.0%	2.4%
Sleep disorder	0.4%	1.3%	0	0.3%		1.2%	0.8%	0.4%	0.8%
Confusional state	0.4%	0.5%	0	0.7%		0.8%	0	0.6%	0.7%
Anxiety	2.7%	2.8%	7.9%	3.3%		2.9%	2.5%	1.6%	2.2%
Impulse control disorder	0	0.2%	0	0.2%		0	0	0	<0.1%
Compulsions	0	0.2%	0	0		0	0	0	<0.1%
Obsessive thoughts	0	0	0	0		0	0.2%	0	<0.1%
Libido increased	0	0.2%	0	0.2%		0	0.4%	0	0

* 82 Of 89 patients (92%) received 200mg of Safinamide

Adverse events with an occurrence rate of ≥5% have been underlined.

2.8.2.3. Impulsive-compulsive disorders

Safinamide also was not associated with an increase in impulsive/compulsive behavior, as assessed by the QUIP (Parkinson's Disease Impulsive-Compulsive Disorders Questionnaire, a self-administered questionnaire specifically designed to assess the severity of symptoms of impulse control disorders (e.g. pathological gambling, buying, eating, and sexual behaviour) in patients with Parkinson's disease. The QUIP was performed in two studies: Study 27918 (MOTION) and 27919 (SETTLE). Data analysed from overall Group 1 safety population of MOTION and SETTLE showed that changes from baseline in the QUIP scale were similar in the safinamide and placebo groups.

Among all subjects who received safinamide, 272 subjects (74.5%) showed no compulsive behaviour at baseline, as evaluated by the QUIP Scale; 49 subjects (13.4%) displayed one act of a compulsive behaviour and 44 subjects (12.1%) displayed 2 or more acts of compulsive behaviour at baseline. Post-baseline evaluations indicated no significant changes, showing that 55 subjects (15.1%) had one act of a compulsive behaviour and 46 (12.6%) displayed 2 or more acts of compulsive behaviour as worst post-baseline values.

The incidence is similar to placebo patients. Similar shifts from baseline to worst post-baseline evaluations were observed in safinamide treatment groups, to those seen in the placebo group.

Table 34 Incidence of Impulsive-Compulsive disorders

Time point	Category	Safinamide	All placebo
		N= 727	N=500
Baseline value	None	74.5%	75.0%
	1 Compulsive behaviour	13.4%	13.3%
	≥2 Compulsive behaviours	12.1%	11.7%
Worst post-baseline value			
	None	72.3%	69.5%
	1 Compulsive behaviour	15.1%	14.5%
	≥2 Compulsive behaviours	12.6%	16.0%

2.8.2.4. Gastro-intestinal adverse events

Between 22- 29% of the patients experienced gastro-intestinal adverse events. Nausea and constipation were the most common gastro-intestinal adverse events. The numeric occurrence rate of nausea was higher for ESPD patients (6.2-10.1%) compared to LSPD patients (4.1-6.5%). About 4.3% of the patients from Group 2 experienced nausea. For both ESPD and LSPD patients, nausea was more likely to occur with increasing dosages of safinamide. The same applies to vomiting. By contrast, diarrhoea was experienced less frequently with increasing doses of safinamide in both ESPD and LSPD patients.

Constipation was experienced by 5-8.2% of LSPD patients compared to less than 5% of ESPD patients.

Table 35 Summary of gastro-intestinal TEAEs for Safinamide

	Placebo-controlled studies (Group 1)								**Open label studies (Group 2)**
	ESPD					**LSPD**			
	Safinamide (mg/day)			**Placebo**		**Safinamide (mg/day)**		**Placebo**	
	50	100	150-200*			50	100		
Number of patients	282	424	89	422		243	478	497	1025
Gastro-intestinal disorders	21.6%	24.8%	29.2%	25.1%		26.7%	26.4%	21.5%	20.5%
Nausea	6.2%	9.6%	10.1%	7.1%		4.1%	6.5%	4.8%	4.3%
Diarrhoea	4.3%	3.8%	1.1%	4.5%		4.1%	2.5%	2.4%	3.3%
Vomiting	1.1%	2.8%	4.5%	3.8%		1.6%	2.7%	1.8%	1.5%
Abdominal pain	1.8%	1.9%	0	2.1%		2.5%	1.3%	1.4%	1.5%
Constipation	2.8%	2.4%	4.5%	3.3%		8.2%	6.1%	5.0%	5.0%

* 82 Of 89 patients (92%) received 200mg of Safinamide

Adverse events with an occurrence rate of ≥5% have been underlined

The higher occurrence rate of constipation among LSPD patients compared to ESPD patients probably partly reflects a disease-associated higher occurrence rate of constipation in LSPD.

2.8.2.5. Cardiovascular adverse events

The occurrence of vascular disorders increased with the dose in ESPD patients (6.4% for 50mg Safinamide; 13.5% for 100mg Safinamide). This applies to both hypertension and orthostatic hypotension.

The occurrence of orthostatic hypotension increases with increasing doses of Safinamide (2.1% for 50mg Safinamide; 2.5% for 100mg Safinamide). A reverse trend was observed for the occurrence of hypertension (8.2% for 50mg Safinamide; 4.8% for 100mg Safinamide). Arrhythmia and bradycardia occurred in less than 0.5% of patients.

Table 36 Summary of cardiovascular TEAEs for Safinamide

	Placebo-controlled studies (Group 1)								Open label studies (Group 2)
	ESPD					LSPD			
	Safinamide (mg/day)			Placebo		Safinamide (mg/day)		Placebo	
	50	100	150-200*			50	100		
Number of patients	282	424	89	422		243	478	497	1025
Any adverse event	68.4 %	72.4 %	66.3 %	73.0 %		88.5 %	79.3 %	78.3 %	73.1%
Vascular disorders	6.4%	7.8%	13.5 %	8.3%		12.3 %	9.0%	8.2%	6.0%
Hypertension	1.9%	4.3%	9.0%	3.5%		8.2%	4.8%	3.8%	2.0%
Orthostatic hypotension	1.9%	1.0%	4.5%	0.5%		2.1%	2.5%	2.0%	1.3%
Hypotension	0.4%	1.0%	1.1%	1.8%		2.5%	0.6%	1.6%	0.8%
Cardiac disorders	6.4%	3.1%	6.7%	4.7%		4.9%	4.2%	4.4%	4.9%
Bradycardia	0.4%	0	0	0		0	0.2%	0	0.4%
Arrhytmia	0.4%	0	0	0		0.4%	0.4%	0.2%	<0.1%

* 82 Of 89 patients (92%) received 200mg of Safinamide

Adverse events with an occurrence rate of ≥5% have been underlined

Although the incidence of bradycardia and arrhythmia as adverse events was slightly higher in the active treatment arms as compared to placebo, there was no clear signal of abnormalities from the ECGs, which were routinely monitored in the therapeutic clinical trials. There was no evidence of effect of safinamide on ECGs from the therapeutic clinical trials. In a randomized, double blind, placebo-controlled study in healthy subjects (trial 28559) the effects of Safinamide (100 and 350mg) on the QT/QTc interval have been investigated with Moxifloxacine (400mg) as a positive control. Safinamide was not associated with QTc prolongation in this trial. By contrast, in both the Moxifloxacin and supratherapeutic Safinamide group a mild PR shortening was observed (<4 msec for both groups). This level of effect, if caused by the drug, was considered of no clinical relevance.

2.8.2.6. Skin and subcutaneous tissue disorders

For ESPD, the occurrence of skin and subcutaneous disorders decreased with increasing Safinamide dosage (50mg 11.7%; 150-200mg 4.5%). For LSPD patients, the occurrence rate was similar for 50 and 100mg Safinamide: 11.5%. These rates were higher compared to placebo (9.9%).

In the open label studies 10% of patients experienced skin and subcutaneous tissue disorders. In this patient group, one patient experienced a melanoma. In the double-blind placebo-controlled trials none of the patients experienced melanoma.

2.8.2.7. Ocular adverse events

In repeated-dose studies with Safinamide in rats retinal degeneration has been observed. In the chronic studies, these retinal alterations progressed to a stage where the outer nuclear layer disappeared and changes to the pigment epithelium. Loss of nuclei from the inner nuclear layer was also present. The lowest dose producing retinal atrophy was 15mg/kg/day. Thus far, these changes have not been noted in any human or non-human primate species in which ocular investigations have been performed.

Once the potential of retinal degeneration had been observed, it was decided to introduce ocular investigations for the patients enrolled in the safinamide development program. Ocular examinations included: visual acuity, LogMAR assessment (chart to determine visual acuity), colour vision examination, funduscopy assessment, visual field assessment, global impression score of ocular function, occurrence of ocular TEAEs, ocular coherence tomography (OCT), and electroretinograms (ERG). The extent to which this was done differed between studies and research sites. Ocular images were assessed centrally by a neuro-ophthalmologist.

As represented in the next Table 37, 30 retinal degeneration was observed in 2.2% of ESPD patients treated with 150-200mg per day in Study 017, in which there were no baseline ocular assessments. Retinal degeneration has not been observed in other ESPD patients. Retinal degeneration (LSPD patients) was observed in 2.1% of patients treated with 50mg safinamide per day and in 0.2% of patients who received 100mg safinamide per day. Also one placebo-treated patient experienced retinal degeneration (0.2% from the Placebo group).

Cataract occurred in 3.5-5.6% of ESPD patients, compared to 6.3-14% of LSPD patients.

Conjunctivitis occurred in less than 2% of both ESPD and LSPD patients.

Table 37 Summary of ocular TEAEs for Safinamide

	Placebo-controlled studies (Group 1)								**Open label studies (Group 2)**
	ESPD					**LSPD**			
	Safinamide (mg/day)			**Placebo**		**Safinamide (mg/day)**		**Placebo**	
	50	100	150-200 *			50	100		
Number of patients	282	424	89	422		243	478	497	1025
Eye disorders	13.1%	16.0%	19.1%	14.5%		27.2%	15.9%	18.5%	10.9%
Cataract	3.2%	3.1%	5.6%	3.1%		14.0%	6.3%	6.4%	4.1%
Retinal degeneration	0	0	2.2%	0		2.1%	0.2%	0.2%	0
Conjunctivitis	1.1%	1.4%	0	0.7%		0	0.4%	0.6%	0.6%

* 82 Of 89 patients (92%) received 200mg of Safinamide

Adverse events with an occurrence rate of ≥5% have been underlined

Ophthalmological examination

As mentioned above, different ophthalmological assessments have been performed in a limited number of patients in different studies over time after the non-clinical findings were known. A number of these assessments have been done in studies 015 and 017, study 016 and 018, Motion, and SETTLE. In these studies, assessment results were similar for safinamide and placebo treatment.

Ocular coherence tomography outcomes in ESPD:

In study 27918 (MOTION) the change in thickness of the retinal nerve fiber layer (RNFL) in ESPD patients has been determined by OCT. The mean change in RNFL thickness for the dosage of 50mg safinamide/day was -0.4(SD 4.9) micrometre for the left eye and 0.2(SD 3.7) micrometre for the right eye. For the dosage of 100mg safinamide/day and placebo treatment these mean changes for the left and right eye were -1.2 (SD 5.2) and -1.9 micrometre (SD 3.6) and 1.5 (SD 4.2) and 0.8 (SD 3.8) micrometre respectively.

In the same study, there was also no significant change in total macula volume in either eye during safinamide or placebo treatment. An analysis of electroretinograms of 20 patients did not detect any treatment-related adverse change for safinamide compared with placebo.

ESPD patients who completed the MOTION study entered a double-blind, placebo-controlled extension phase (study 27938, MOTION EXTENSION) and were treated for up to 18 months. Ophthalmological examinations were repeated at periodic intervals. The mean change in RNFL thickness (SD) compared to baseline for the left eye in the 50mg safinamide, 100mg safinamide, and placebo were: -0.1 (5.8), -1.1(5.3), and 1.0(5.4). The respective changes for the right eye were: -0.8 (4.5), -1.2 (4.6), and -0.9(5.1). Also for the change in OCT total macula volume (cubic mm) no significant changes have been observed in these studies.

Table 38 Change from baseline in OCT parameters in ESPD in Motion extension study (18 months)

			Safinamide				**Placebo**	
			50mg/day		**100mg/day**			
	N		**174**		**179**		**154**	
Time point	**Eye**		**Value**	**Change**	**Value**	**Change**	**Value**	**Change**
RNFL thickness (micrometre)								
Baseline	**Left**	**N (missing)**	42 (132)		42 (137)		31 (123)	
		Mean±SD	93.5±10.9		92.9±13.8		94.9±10.1	
	Right	**N (missing)**	41 (133)		38 (141)		30 (124)	
		Mean±SD	93.9±11.1		94.9±14.4		95.7±10.6	
Extension endpoint (max 18 months)	**Left**	**N (missing)**	51 (123)	34 (140)	57 (122)	33 (146)	43 (111)	21 (133)
		Mean±SD	93.1±11.0	-0.1±5.8	92.7±12.5	-1.1±5.3	95.9±13.3	1.0±5.4
	Right	**N (missing)**	50 (124)	32(142)	59 (120)	30 (149)	45 (109)	21 (133)
		Mean±SD	91.9±11.7	-0.8±4.5	92.8±11.7	-1.2±4.6	99.0±12.6	-0.9±5.1
Total macula volume (cubic mm)								
Baseline	**Left**	**N (missing)**	**50 (124)**		**53 (126)**		**43 (111)**	
		Mean±SD	8.22±1.62		7.85±1.61		8.00±1.56	
	Right	**N (missing)**	52 (122)		55 (124)		40 (114)	

			Safinamide				Placebo	
			50mg/day		100mg/day			
	N		174		179		154	
Time point	Eye		Value	Change	Value	Change	Value	Change
		Mean±SD	8.16±1.58		7.99±1.63		7.89±1.50	
Extension endpoint (max 18 months)	Left	N (missing)	53 (121)	40 (134)	70 (109)	44 (135)	51 (103)	34 (120)
		Mean±SD	8.25±1.61	-0.07±0.23	8.47±1.72	0.08±0.40	8.06±2.08	-0.13±0.82
	Right	N (missing)	56 (118)	42 (132)	66 (113)	42 (137)	52(102)	31 (123)
		Mean±SD	8.30±1.64	-0.03±0.19	8.48±1.70	0.06±0.36	8.11±2.08	-0.13±0.79

OCT parameters in LSPD

For LSPD, ophthalmological parameters have been determined in a limited number of patients in study 27919 (SETTLE). This study had a duration of 6 months. In this study no significant differences between Safinamide and placebo treatment have been observed with respect to the parameters visual acuity, logMAR assessment, colour vision, funduscopy, and visual field.

In the SETTLE study also the RNFL thickness (micrometre) and total macula volume (cubic mm) have been determined. These analyses showed a reduction of -0.9 and -1.0 for the left and right eyes, respectively, for Safinamide, and an increase of 0.1 in the right eye, but a reduction of -0.2 in the left eye for the placebo group.

Results for changes in total macular volume were similar for Safinamide and placebo. Small mean reductions (-0.03 to -0.07) were observed for both the right and left eyes in both groups, indicating no effect of safinamide treatment.

Table 39 Change from baseline in OCT parameters in LSPD in Motion extension study (24 weeks)

			Safinamide		Placebo	
	N		274		275	
Timepoint	Eye		Value	Change	Value	Change
RNFL thickness (micrometre)						
Baseline	Left	N (missing)	77 (197)		80 (195)	
		Mean±SD	96.1±11.4		95.4±11.3	
	Right	N (missing)	84 (190)		82 (193)	
		Mean±SD	94.5±11.9		96.0±12.4	
Week 24	Left	N (missing)	90 (184)	61 (213)	85 (190)	57 (218)
		Mean±SD	94.6±12.0	-0.9±4.2	94.6±11.1	0.1±5.5
	Right	N (missing)	92 (182)	65 (209)	84 (191)	61 (214)
		Mean±SD	94.7±11.9	-1.0±5.9	95.4±11.3	-0.2±4.7
Total macula volume (cubic mm)						
Baseline	Left	N (missing)	92 (182)		92 (182)	
		Mean±SD	8.57±1.63		8.41±1.56	
	Right	N (missing)	93 (181)		96 (179)	
		Mean±SD	8.54±1.69		8.43±1.54	
Week 24	Left	N (missing)	95 (179)	68 (206)	91 (184)	69 (206)
		Mean±SD	8.45±1.66	-0.03±0.18	8.49±1.66	-0.03±0.77
	Right	N (missing)	101 (173)	72 (202)	94 (181)	73 (202)
		Mean±SD	8.54±1.69	-0.05±0.32	5.55±1.65	-0.07±0.74

2.8.2.8. Adverse events by age

Approximately 25% of ESPD and LSPD patients were under 55 years of age. Between 3.2 and 7.9% of ESPD patients were 75 years of age or older compared to 3.7 to 4.0% of LSPD patients. The majority of included patients (about 70%) were 55 to 75 years of age.

The occurrence of adverse events during safinamide treatment was higher than during placebo treatment among patients aged ≥75 years or above. This was seen for both ESPD (86.2-100% vs. 59.1%) and LSPD (88.9-94.4% vs. 70.0%). Only in the oldest age group there was some evidence of a safinamide-dose dependent increase in occurrence of adverse events. The occurrence of adverse events per treatment dose increased with age in ESPD patients, but not in LSPD patients.

Table 40 Summary of overall incidence of adverse events by age

	Placebo-controlled studies (Group 1)								Open label studies (Group 2)
	ESPD					LSPD			
	Safinamide (mg/day)			Placebo		Safinamide (mg/day)		Placebo	
	50	100	150-200 *			50	100		
Number of patients	282	424	89	422		243	478	497	1025
Any adverse event	68.4%	72.4%	66.3%	73.0%		88.5%	79.3%	78.3%	73.1%
Any adverse event within a particular age group									
< 55 years	59.7%	74.8%	58.1%	79.5%		93.5%	78.3%	73.3%	**
55-75 years	71%	70.0%	66.7%	71.5%		86.6%	78.8%	80.3%	**
>= 75 years	88.9%	86.2%	100%	59.1%		88.9%	94.4%	70.0%	**

* 82 Of 89 patients (92%) received 200mg of Safinamide

** Not determined

ESPD

For subjects in the <55 years age category, the most commonly reported TEAE was somnolence and the incidence of migraine, motor dysfunction, paresthesia, dyspepsia, abdominal pain, constipation, upper respiratory tract infection, arthralgia, muscle spasms, sleep disorder, blood creatinine, increased, blood glucose increased, protein urine present, WBCs urine positive, joint injury, limb injury, orthostatic hypotension, and micturition urgency was 2-fold higher in the combined safinamide group compared with the combined placebo group.

For subjects in the 55-to-75 years category, the most commonly reported TEAE was back pain and the incidence of sciatica, visual field defect, rhinitis, chest pain, and decreased appetite was 2-fold higher in the combined safinamide group.

For subjects in the >75 years age category, the most commonly reported TEAE was headache and the incidence of approximately one-quarter of the reported TEAEs was 2-fold higher in the combined safinamide group due to the relatively small number of subjects in the combined placebo group in this age category (n = 22).

LSPD

The most commonly reported TEAE was dyskinesia, which had an incidence that was about 2-fold higher in the combined safinamide group compared to the placebo group, for all three age categories; <55 years age category (safinamide: 30%; placebo: 17%), 55-to-75 years age category (safinamide: 23%; placebo: 12%), and >75 years age category (safinamide: 19%; placebo: 0%).

For subjects in the <55 years age category, back pain, pyrexia, and insomnia also had an incidence that was 2-fold higher in the combined placebo group.

For the 55-to-75 years age category, the incidence of hypoesthesia, muscle rigidity, protein urine present, anxiety, and cough was 2-fold higher in the combined safinamide group.

For subjects in the >75 years age category, the incidence of most of the reported TEAEs was 2-fold higher in the combined safinamide group due to the relatively small number of subjects in this age category in the combined safinamide group (n = 27) and the combined placebo group (n = 20).

2.8.3. Serious adverse event/deaths/other significant events

ESPD

For the Group 1 ESPD population, serious adverse events (SAEs) reported in 2 or more safinamide-treated subjects were osteoarthritis (3; 0.4%; 50 mg/day), angina pectoris (2; 0.3%; 100 mg/day), atrial fibrillation (2; 0.3%; 50 mg/day), coronary artery disease (2; 0.3%; 100 mg/day), myocardial infarction (2; 0.3%; 50 mg/day), depression (2; 0.3%; 100 mg/day), visual hallucination (2; 0.3%; 50 mg/day, 150-200 mg/day), urinary tract infection (2; 0.3%; 100 mg/day, 150-200 mg/day), and cholelithiasis (2; 0.3%; 50 mg/day).

For the Group 1 ESPD placebo population, the only SAE reported more than once was prostate cancer (2; 0.5%).

LSPD

For the Group 1 LSPD population, SAEs reported in 3 or more safinamide-treated subjects were fall (11; 1.5%; 50 mg/day [2], 100 mg/day [9]), Parkinson's disease (5; 0.7%; 50 mg/day [2], 100 mg/day [3]), sepsis (4; 0.6%; 50 mg/day [1], 100 mg/day [3]), cataract (4; 0.6%; 50 mg/day [2], 100 mg/day [2]), anaemia (4; 0.6%; 100 mg/day), femur fracture (3; 0.4%; 50 mg/day [2], 100 mg/day [1]), myocardial infarction (3; 0.4%; 50 mg/day [1], 100 mg/day [2]), cataract operation (3; 0.4%; 50 mg/day [1], 100 mg/day [2]). Dyskinesia was reported in only 1 (0.1%, 50 mg/day) subject.

For the **Group 1 LSPD** placebo population, SAEs reported in 3 or more subjects were fall (5; 1.0%), dyskinesia (4; 0.8%), pyrexia (4; 0.8%), cellulitis (3; 0.6%), diarrhoea (3; 0.6%), depression (3; 0.6%), and hallucination (3; 0.6%).

Group 2

For the Group 2 population, SAEs reported in 3 or more subjects were inguinal hernia (9; 0.9%),pneumonia aspiration (6; 0.6%), sudden death (5; 0.5%), femoral neck fracture (5; 0.5%), osteoarthritis (5; 0.5%), femur fracture (4; 0.4%), dyskinesia (4; 0.4%), Parkinson's disease (4; 0.4%), cellulitis (4; 0.4%), hallucination (4; 0.4%), cardiac failure (4; 0.4%), hyponatremia (4; 0.4%), cataract (4; 0.4%), benign prostatic hyperplasia (4; 0.4%), fall (3; 0.3%), abdominal pain (3; 0.3%), diarrhoea (3; 0.3%), cerebrovascular accident (3; 0.3%), convulsion (3; 0.3%), pulmonary embolism (3; 0.3%), acute myocardial infarction (3; 0.3%), prostate cancer (3; 0.3%), hypoglycaemia (3; 0.3%), and urinary retention (3; 0.3%).

Serious adverse events reported the most are summarised in the next Table 41. The occurrence rate for each particular serious adverse event was <2%.

Table 41 Serious adverse events

	Placebo-controlled studies (Group 1)								Open label studies (Group 2)
	ESPD					LSPD			
	Safinamide (mg/day)			Placebo		Safinamide (mg/day)		Placebo	
	50	100	150-200*			50	100		
Number of patients	282	424	89	422		243	478	497	1025
Any serious adverse event	7.1%	6.6%	7.9%	5.0%		14.0%	12.3%	11.5%	14.9%
Fall	0	0	0	0.2%		0.8%	1.9%	1.0%	0.3%
Dyskinesia	0	0	0	0		0.4%	0	0.8%	0.4%
Dizziness	0.4%	0	0	0		0	0.2%	0	<0.1%
Anemia	0	0.2%	0	0.2%		0	0.8%	0.2%	<0.1%
Seizure	0	0	0	0		0	0	0	0.3%
Depression	0	0.5%	0	0		0.4%	0.2%	0.6%	<0.1%
Liver disorder	0	0	0	0.2%		0.4%	0	0	0
Sepsis	0	0	0	0		0.4%	0.6%	0.4%	0.2%
Atrial fibrillation	0.7%	0	0	0.2%		0	0	0	0
Myocardial infarction	0.7%	0	0	0		0.4%	0.4%	0	0.2%
Atrial flutter	0	0.2%	0	0		0	0	0	0
Ventricular tachycardia	0.4%	0	0	0		0	0.2%	0	0

* 82 Of 89 patients (92%) received 200mg of Safinamide

Deaths

Mortality during the safinamide development program was determined during use of study medication, or within 30 days after last dose of study medication. In addition deaths that occurred more than 30 days after discontinuation of study medication, were included if the adverse event that led to the fatal outcome had an onset within 30 days of the final dose of study medication.

A total of 61 patients died. The crude mortality rate during safinamide treatment was 2.6% (1.7 per 100 person years) and during placebo treatment was 1.2% (1.3 per 100 person years). Most frequent causes of death were cardiac disorders, general disorders, infections and infestations:

Table 42 Summary of deaths by treatment – all studies

Treatment	Subjects	Deaths	Incidence rate (%)	Person time (years)	Mortality rate per 100 person years
Safinamide	1949	50	2.6	3021.6	1.7
Placebo	919	11	1.2	863.2	1.3

Mortality in placebo-controlled studies.

The mortality rate among ESPD patients was 0.50% among Safinamide-treated patients and 0.24% among placebo-treated patients.

The respective rates for LSPD patients were 2.50% and 2.01%.

Mortality rates tended to increase with increasing Safinamide dosages:

Table 43 Mortality in ESPD and LSPD studies

		Safinamide (mg/day)				Placebo
	Dose (mg/day)	**50**	**100**	**150-200**	**Overall**	
ESPD	Number of exposed patients	282	424	89	795	422
	Deaths	1	2*	1	4*	1
	Percentage	**0.35%**	**0.47%**	**1.12%**	**0.50%**	**0.24%**
LSPD	Number of exposed patients	243	478	0	721	497
	Deaths	5	13	0	18	10
	Percentage	**2.06%**	**2.72%**	**0**	**2.50%**	**2.01%**
Total ESPD and LSPD patients	Number of exposed patients	525	902	89	1516	919
	Deaths	6	15*	1	22*	11
	Percentage	**1.14%**	**1.66%**	**1.12%**	**1.45%**	**1.20%**

***** Including 1 patient who died 39 days after the last dose of study medication.

The mortality rate in the open-label studies (Study 28850 and open-label phase of Study 024) in which all patients received safinamide was 2.7% (28 of 1025) patients. For the open-label studies the adjusted mortality rate per 100 years of exposure was 1.3 (CIs 1.27-1.37).

2.8.4. Laboratory findings

Haematology

Safinamide had no relevant effect on haematological parameters.

Table 44 Shifts of Hematology Laboratory Values by Worst Post-Baseline Value by Treatment Group of LSPD Patients, Completed Phase 2 and Phase 3 Controlled Trials – Safety Population

Category	Safinamide treatment groups		All safinamide treatment groups (n=721) n (%)	Placebo (n=497) n (%)
	50 mg/day (n=243) n (%)	100 mg/day (n=478) n (%)		
Subjects with shifts to clinically significant below normal				
Basophils (10^9/L)	0	0	0	0
Eosinophils (10^9/L)	0	0	0	0
Haematocrit (Proportion of 1.0)	16/238 (6.7)	19/471 (4.0)	35/709 (4.9)	30/492 (6.1)
Leukocytes (10^9/L)	4/238 (1.7)	1/472 (0.2)	5/710 (0.7)	3/492 (0.6)
Lymphocytes (10^9/L)	0	31/267 (11.6)	31/274 (11.3)	30/275 (10.9)
Monocytes (10^9/L)	0	0	0	0
Neutrophils (10^9/L)	0	0	0	0

Chemistry

There was a small increase in AST levels at safinamide treatment. However, this was not associated with a change of other liver function parameters like ALT, bilirubin or GGT. Overall, the number of patients with clinically relevant changes in liver function was low and similar between safinamide and placebo (see Table 45 below).

Table 45 Number of subjects with clinically relevant changes of liver functions test from baseline in LSPD patients

Category	Safinamide treatment groups		All Safinamide treatment groups (n=721) n (%)	Placebo (n=497) n (%)
	50 mg/day (n=223) n (%)	100 mg/day (n=498) n (%)		
Subjects with shifts to clinically significant above normal				
Alkaline phosphatase (U/L)	2/195 (1.0)	0	2/640 (0.3)	0
Alanine aminotransferase (IU/L)	1/208 (0.5)	0	1/681 (0.1)	1/471 (0.2)
Aspartate aminotransferase (IU/L)	1/196 (0.5)	0	1/658 (0.2)	1/472 (0.2)
Bilirubin (umol/L)	1/187 (0.5)	0	1/645 (0.2)	3/454 (0.7)
Gamma glutamyl transferase (IU/L)	1/177 (0.6)	3/416 (0.7)	4/593 (0.7)	2/433 (0.5)
Lactate dehydrogenase (IU/L)	0	0	0	1/466 (0.2)

A significant increase in creatine kinase has been observed in Late Stage PD patients. However, this was not observed in early PD patients. The raise in creatine kinase levels in the advanced PD patients might be a symptom of increased dyskinesia rates in this population. There were no signals of decreased renal function.

2.8.5. Safety in special populations

Pregnancy and lactation

Female ESPD and LSPD patients of childbearing potential were excluded from study participation if they were found to be pregnant (serum and urine pregnancy tests were performed at visits specified in the protocols). Non-pregnant included patients received contraception beginning four weeks prior to enrolment, and continuing throughout the treatment period and for four weeks after the last dose of the study medication. It is not known if safinamide is excreted via breast milk; therefore, breastfeeding females were not included into studies.

Since no pregnant and/or lactating ESPD and LSPD patients have been included in the development program of safinamide, the effects of safinamide in these human subjects are yet unknown. The main target population of advance PD patients consist of elderly women with no childbearing potential.

Other special populations

The safety of safinamide has not been determined in other special populations such as patients with severe cardiovascular disease, renal or liver insufficiency. Chronic non-life threatening concomitant disease was a contra-indication for study participation in different trials. For example, patients with a current diagnosis of clinically significant gastrointestinal, renal, hepatic, endocrine, pulmonary or cardiovascular disease, including acute gastric ulcer, hypertension that is not well-controlled, cardiac

conditions (e.g. uncontrolled atrial fibrillation, recent myocardial infarction), asthma, chronic obstructive pulmonary disease (COPD), and Type I diabetes were not eligible for participation in the MOTION study.

2.8.6. Discontinuation due to AES

Less than 5% of ESPD and LSPD patients discontinued treatment due to adverse events. 2.4% Of Safinamide-treated Group1 ESPD patients discontinued treatment for this reason compared to 3.3% of placebo-treated ESPD patients in this group.

Among LSPD patients, treatment discontinuation due to adverse events was higher upon safinamide treatment compared to placebo treatment (3.7 vs. 2.4%). The most common adverse events among Safinamide-treated LSPD patients were: dyskinesias, dizziness, paraesthesias, asthenia, visual hallucinations, and vomiting (see Table 41).

Table 46 Treatment emergent adverse events leading to treatment discontinuation

	Randomized trials (Group 1)				**Open label**
	ESPD		**LSPD**		**ESPD+ LSPD**
	Safinamide	Placebo	Safinamide	Placebo	
Number of patients per treatment group	795	422	721	497	1025
Subjects with at least one adverse event lading to treatment discontinuation	2.4%	3.3%	3.7%	2.4%	2.0%
Most frequently reported events (≥2 reports) leading to discontinuation, descending in Safinamide-treated Group 1 LSPD-patients					
Dyskinesias	0	0	1.1%	0.2%	<0.1%
Dizziness	0	0.2%	0.3%	0.2%	<0.1%
Paraesthesia	0	0	0.3%	0	0
Asthenia	0	0	0.3%	0	0
Visual hallucination	0.1%	0	0.3%	0	0
Vomiting	0.1%	0	0.3%	0	0

2.8.7. Discussion on clinical safety

Efficacy and safety of safinamide treatment have been evaluated in different randomized, double-blinded clinical trials with a maximum duration of 24 months, as well as open label studies.

Patients included in the studies concerned otherwise relatively healthy patients with Parkinson's Disease. Patients with serious chronic systemic diseases (like e.g. severe hepatic disease) were excluded and the SmPC was adapted to reflect this by introducing appropriate contraindications in section 4.3. -

Between 66% and 89% of all patients experienced adverse events. Studies in the development program show that the occurrence of adverse events increased with advancing age in safinamide-treated patients. ESPD patients experienced fewer adverse events than LSPD patients although differences were not large. Serious adverse events were nearly twice as common among safinamide-treated LSPD patients compared to safinamide-treated ESPD patients (12-14% vs. 7-8%). Less than 0.5% of ESPD patients died during follow-up compared to 2-2.5% of LSPD patients, which might be due to the fact that advanced PD patients are overall more vulnerable.

From a safety perspective, more adverse events would have been expected with the increase of the dose of safinamide. However neither in the ESPD nor in the LSPD patient population there was a consistent dose-effect relationship regarding specific adverse events.

The most frequently observed adverse events among ESPD patients concerned nervous system disorders (27-33%), gastro-intestinal disorders (22-29%), infections and infestations (19-29%) and musculoskeletal and connective tissue disorders (19-24%). The most frequently observed types of adverse events among LSPD patients were: nervous system disorders (38-60%), gastro-intestinal disorders (22-27%), infections and infestations (18-22%), musculoskeletal disorders (20-30%), and eye disorders (16-27%).

Frequently occurring neurological adverse events in both ESPD and LSPD patients were: dizziness, headache, somnolence and tremor. Dyskinesias have been observed more frequently in LSPD patients as compared to ESPD patients (13-31% vs. 0-0.2%) and probably were dependent on the disease stage and/or the use of L-dopa. The increased incidence of dyskinesias among LSPD patients was not considered to be a major issue since dyskinesias are normally associated with an increase in ON time and were usually mild. The provided data about any increase in ON time without dyskinesias and ON-time with troublesome dyskinesia, in order to better assess the pros and cons of dyskinesia as an adverse event, confirmed that the overall incidence of troublesome dyskinesia was low and not different in the study arms.

About 15-20% of the ESPD and LSPD patients experienced psychiatric adverse events. The general occurrence rates for both ESPD and LSPD patients tended to decrease with the increase in safinamide dose. The most frequently observed psychiatric adverse events in both ESPD and LSPD patients were: insomnia, depression, anxiety, and hallucination.

Impulse control disorders and hyper sexuality disorders occurred in less than 0.5% of patients. For levodopa, psychiatric adverse events have been reported in 25% of patients.

Nausea and constipation were frequently seen in both ESPD and LSPD patients

Contrary to most other adverse events, the occurrence orthostatic hypotension tended to increase with increasing doses of safinamide in both ESPD and LSPD patients (ESPD 1.9-4.5%, LSPD 2.1-2.5%). Given the low incidence though it was not considered justified to conclude on a dose relationship.

Between 3 and 6% of ESPD patients experienced cataract, compared to 6-14% of LSPD patients.

Safinamide treatment was associated with increased ASAT enzymes, though this was often self-limiting, and ALT and bilirubin remained stable. One of the important questions to be addressed was whether the incidence of adverse events increased with long-term exposure, or with age. Pooled safety data presenting the incidence and prevalence of adverse events for three different time periods of exposure (0-6 months, 6-12 months, and ≥12 months) were submitted, and demonstrated that the incidence of adverse events decreased over exposure time and that there was no evidence of new adverse events emerging with duration of exposure. It was noted that a limited number of older people was included in the trial, whereas the rate of adverse events increased with age. In the Risk Management Plan, the use in the older people is included as an important "missing information", and will have to be further addressed in future PSURs.

The adverse events for different combinations of polytherapy (L-Dopa alone, L-Dopa + Dopamine agonist, or L-Dopa + Dopamine agonist + amantadine), were also assessed and no different patterns of frequency or type of adverse events were observed.

The results of the cardiological examinations were difficult to interpret since only changes in conduction times between start and end of the study have been reported instead of the frequency of abnormal conduction times prior to and after treatment. However, since there was no signal of cardiovascular events in the trials, and safinamide does not prolong QTc in a dedicated study, this was no considered a major problem.

After retinal degeneration had been observed in rats upon use of safinamide-treatment, ophthalmological examinations were introduced in the safinamide development program. Retinal degeneration has was observed in 2.2% of patients in the 150-200 mg/day group in Study 015, where there were no baseline ocular assessments, but has not been observed in other studies with treatment for longer duration. Systematic ophthalmological monitoring did not detect a risk of retinal degeneration in patients as compared to placebo, up to a period of 2 years.

The CHMP agreed that the data provided from the ocular safety report did not indicate that there was a significant ocular safety issue. The most important parameters for evaluating potential effects of safinamide on the retina are the retinal nerve fiber layer (RNFL) thickness and total macular volume as measured by Optical Coherence Tomography (OCT) as changes in these parameters precede abnormalities in fundoscopy, colour vision, visual acuity. Results for RNFL and total macular volume were highly inconsistent and did not point at an unfavourable effect of safinamide in a period of 1.5-2 years. Up to moment of assessment the OCT data did not indicate a problem that might preclude approval. However, ophthalmic safety and retina degeneration will remain subject of special interest in future PSURs. The Applicant has made a commitment to develop targeted questionnaires, which will allow the collection of information from spontaneous cases in a structured manner.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

2.8.8. Conclusions on the clinical safety

Overall the safety of safinamide was considered acceptable, as incidences of adverse events under safinamide treatment seemed quite low as compared to placebo. In the light of the animal findings, the CHMP was of the view that even though the clinical data did not indicate a risk in Parkinson's disease patients, retinal deterioration should be considered as an important potential risk and followed up through the proposed routine and additional pharmacovigilance activities, as described in the RMP. Targeted questionnaires should be developed to facilitate future safety surveillance.

2.9. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.10. Risk Management Plan

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 9 is acceptable.

During this procedure, in the period after the finalisation of the PRAC outcome and before the CHMP Opinion, certain changes were agreed regarding two issues:

-The inclusion of retinal degeneration as a potential risk with all appropriate sections amended accordingly.

-The reflection of the two pharmacokinetic studies (*in vitro* study on amidase enzymes involved in the biotransformation of safinamide to NW-1153 and DDI study with a BCRP substrate with a Tmax < 2 hours), both as category 3 and with a proposed date of submission of July 2015.

The CHMP endorsed the Risk Management Plan version 9 with the following content:

Table 47 Safety concerns

Summary of safety concerns	
Important identified risk:	Adverse event of Dyskinesia in mid/late PD patients on concomitant use of L-Dopa, alone or in combination with other dopaminergic medication. Increased incidence of ADRs relating to Dyskinesia in Mid-Late Stage PD on L-Dopa could be considered as a risk for patients exposed to safinamide. This is the most common AE in excess of placebo.
	Teratogenicity A comprehensive reproductive toxicity study programme indicates that Safinamide when given alone, or even more so when given in combination with dopaminergic drugs, is predicted to increase the risk of adverse developmental and perhaps reproductive outcomes in humans when used in accordance with the dosing information in the product label. Safinamide therefore should not be given during pregnancy, to lactating women, or to women of childbearing potential not practicing adequate contraception. Women of child bearing potential should be advised not to become pregnant during safinamide therapy.
Important Potential Risks:	Risk of retinal degeneration in patients with PD treated with safinamide Retinal degeneration was observed in rat repeated-dose toxicity studies but not in monkey studies. The species most affected was the rat, in which a time and dose-dependent retinal atrophy was observed both in pigmented and non-pigmented animals. The lowest dose producing retinal atrophy was 15 mg/kg/day. Only mild retinal atrophy occurs in mice after life-time treatment in the carcinogenicity study at the highest dose tested (200 mg/kg/day). Monkeys were not affected by retinal changes (at doses up to 70 mg/kg/day for 39 weeks); this was confirmed by an independent Pathology Working Group. In addition, no retinal changes were induced in monkeys treated for 13-week with combination of safinamide and L-dopa/carbidopa. Similarly, no retinal changes were present in another 13-week monkey combination study with safinamide and pramipexole. The ocular effects of safinamide have been comprehensively evaluated using an ophthalmological examination in ~2000 patients in therapeutic studies, including the measurements of retinal change using Ocular coherence tomography (OCT) in over 300 patients on safinamide, and retinal function using electro-retinogram (ERG) in a single center in a limited number of patients. All results were reviewed by an independent rater blinded to the treatment condition. Review of the data, and detailed statistical analyses did not detect any systematic difference in the incidence of newly abnormal, or worsening ocular function in safinamide treated patients compared to placebo. There was no difference in the incidence of adverse events relating to the

Summary of safety concerns	
	lens or the retina in safinamide treated patients compared to placebo. However, as patients with history of retinal disease, including inherited conditions were excluded from the studies, use of safinamide in these patients is considered a potential risk.
	Use in severe hepatic impairment. Results from the study performed in patients with hepatic dysfunction indicated higher exposures of safinamide, but without any clinically important changes in liver enzymes. These findings led the Sponsor to conclude that safinamide should be contraindicated in patients with severe liver disease, and the maximum dose to be administered to patients with moderate liver disease is limited to 50mg, with the provision that if the liver dysfunction progresses from moderate to severe, the patients should discontinue treatment with safinamide [see SmPC section 4.2, 4.3]. These precautions and warnings, adequately cover the risk for patients with liver disease who may be treated with safinamide.
	Impulse control disorders (ICDs) ICDs can occur in patients treated with dopamine agonists and/or dopaminergic treatments. Some reports of ICDs have also been observed with other MAO-inhibitors. Safinamide treatment has not been associated with any increase in the appearance of ICDs. [See SmPC section 4.4: Special Warnings and Precautions for Use]
	Concomitant use of MAOIs, serotonergic drugs, and/or pethidine. Serious adverse events, including serotonin syndrome, have been reported with the concomitant use of MAOIs, serotonergic drugs, and/or pethidine. As this may be a class effect, the concomitant administration of XADAGO and pethidine is contraindicated.
Missing information:	Use in patients with history and/or presence of retinal disease
	Use of safinamide in patients aged<30 years and >75 years
	Effects of Overdose
	Patients with severe, disabling peak-dose or biphasic dyskinesia, or with unpredictable or widely swinging fluctuations.
	Patients who have undergone stereotactic surgery as a treatment for Parkinson's disease
	Use in patients with psychiatric illness, specifically psychosis, bipolar disorder, or severe depression
	Long term use >3 years
	The use of safinamide concomitantly with BCRP substrate drugs. A post authorisation study will be performed: until these results are available, a time interval of 5 hours should be kept between dosing of Safinamide and drugs that are BCRP substrates with a Tmax ≤2 hours
	Whether specific inhibitors of the amidases involved in the metabolism of safinamide to NW-1153, may increase the exposure of safinamide

Pharmacovigilance plan

On-going and planned additional PhV studies/activities in the Pharmacovigilance Plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (Completed)	Date of submission of final study report
Drug Utilization Study, cat. 3	To investigate how safinamide is prescribed and	To confirm the risk/benefit profile of Safinamide in	Planned	July 2019

	used in routine clinical practice.	patients aged > 75 years and patients who are concomitantly suffering from psychiatric conditions (specifically psychosis, bipolar disorder, severe depression)		
DDI study with a BCRP substrate with a Tmax < 2 hours, cat. 3	To determine if there is a pharmacokinetic interaction of safinamide and BCRP substrates.	Potential DDI pharmacokinetic interaction	Planned	July 2015
In vitro study on amidase enzymes involved in the biotransformation of safinamide to NW-1153, cat. 3	To identify specific amidases involved in the metabolism of safinamide to NW-1153	Potential DDI pharmacokinetic interaction	Planned	July 2015

Risk minimisation measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Dyskinesia	Warning in SmPC that dyskinesia may occur on safinamide, and may worsen in patients who have pre-existing dyskinesia. SmPC section 4.8 Undesirable effects.	Proposed routine risk minimisation measures are considered adequate.
Teratogenicity	WOCBP women should be advised not to become pregnant during safinamide therapy. Safinamide should not be given during pregnancy, to lactating mothers Safinamide is not be administered to women of child bearing potential (unless practicing adequate contraception), children and adolescents, below 18 years old. WOCBP should be advised not to become pregnant during safinamide therapy. Monitoring for pregnancy and determination of outcome. Listed in SmPC section 4.6	Proposed routine risk minimisation measures are considered adequate.
Risk of Retinal degeneration in PD patients treated with safinamide	Periodic assessment of risk through evaluation of accumulated data on retinal events. To determine the incidence of retinal events in patients treated with safinamide and their possible attribution	Routine PhV activities including completion of targeted follow-up questionnaires for all spontaneous reports of retinal

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
		events to determine their potential association with safinamide A comprehensive list of terms (HLGT and HLT) indicative of retinal degeneration, retinal atrophy and macular degeneration will be updated.
Risk of Retinal degeneration in patients with presence and/or history of retinal disease	Should not be administered to patients with ophthalmological history that would put them at increased risk for potential retinal effects (e.g., albino patients, family history of hereditary retinal disease, retinitis pigmentosa, any active retinopathy, or uveitis). Listed in SmPC Section 4.3 Contraindications and Section 4.4 Special warnings and precautions	Proposed routine risk minimisation measures are considered adequate.
Severe Liver Impairment	SmPC section 4.2 Use in patients with severe hepatic impairment is contraindicated. SmPC Section 4.3 Contraindication Safinamide use in patients with severe hepatic impairment is contraindicated. SmPC Section 4.4 Special warnings and precautions for use Caution should be exercised when initiating treatment with safinamide in patients with moderate hepatic impairment. In case patients progress from moderate to severe hepatic impairment, treatment with safinamide should be stopped.	Proposed routine risk minimisation measures are considered adequate.
Impulse control disorder	SmPC Section 4.4 Special warnings and precautions for use ICDs can occur in patients treated with dopamine agonists and/or dopaminergic treatments. Some reports of ICDs have also been observed with other MAO-inhibitors. Safinamide treatment has not been associated with any increase in the appearance of ICDs. Patients and carers should be made aware of the behavioural symptoms of impulse control disorders that were observed in patients treated with MAO-inhibitors, including cases of compulsions, obsessive thoughts, pathological gambling, increased libido, hypersexuality, impulsive behaviour and compulsive spending or buying.	Proposed routine risk minimisation measures are considered adequate.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Concomitant Use of MAO-inhibitors, serotinergic drugs and /or pethidine	Avoid risk of interaction by ensuring adequate wash-out (7 days). Listed in SmPC Sections 4.3 Contraindications and 4.5 Interaction with other medicinal products and other forms of interaction.	Proposed routine risk minimisation measures are considered adequate.
Use in patients <30 or >75 years of age	None proposed	NA
Effects of overdose	If an important overdose occurs, XADAGO treatment should be discontinued and supportive treatment should be administered as clinically indicated. Listed in SmPC section 4.9 Overdose	Proposed routine risk minimisation measures are considered adequate.
Treatment of patients with severe, disabling peak-dose or biphasic dyskinesia, or with unpredictable or widely swinging fluctuations.	None proposed	NA
Patients who have undergone stereotactic surgery as a treatment for Parkinson's disease	None proposed	NA
Use in patients with psychiatric illness, including psychosis, bipolar disorder, or severe depression	None proposed	NA
Long term use >3 years	None proposed	NA
Use of safinamide concomitantly with BCRP substrate drugs	SmPC Section 4.5 reports the following: "a time interval of 5 hours should elapse between dosing of Safinamide and drugs that are BCRP substrates with a Tmax ≤2 hours"	NA
Inhibition of amidases involved in the metabolism of safinamide to NW-1153, and may increase the exposure of safinamide	None proposed	NA

There are no additional risk minimisation measures.

2.11. Product information

2.11.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

MAO-B inhibitors are established in the treatment of Parkinson's disease and safinamide is a highly selective and reversible MAO-B inhibitor that does not cause a "cheese effect" linked to tyramine rich food. Safinamide has been shown at doses of 40mg, even lower than the minimal recommended dose of 50 mg, to induce a complete blockage of MAO-B activity in platelets. For other MAO-B inhibitors these effects are non-specific and may exert MAO-A antagonism, causing hypertensive crisis at the time of intake of tyramine-rich food. However, the response to tyramine challenge was similar between placebo and safinamide at supra-therapeutic doses, and no specific measures were considered required for the use of safinamide with tyramine-rich food and drinks.

Safinamide as add-on therapy to L-dopa alone or in combination with other PD medications in mid- to late-stage fluctuating patients

The efficacy of safinamide in late stage Parkinson's Disease as add-on therapy to L-dopa was evaluated in two randomised, parallel, double-blind, placebo-controlled studies of 24 weeks, in patients with motor fluctuations at baseline. Safinamide 50-100 mg daily applied as add-on to levodopa, significantly increased the ON-time without troublesome dyskinesia with approximately 30 minutes per day in one study, and 60 minutes in the other study, as compared to placebo. This effect was considered clinically relevant, also taking into account the clinical response that has been reported in the literature for other registered treatment options in this setting.

Maintenance of efficacy of the ON-time was established in a placebo-controlled extension phase of 24 months. The treatment effect was overall more robust in the 100 mg dose arm: Several post hoc defined responders rates, e.g. 30 minutes improvement in ON with no increase in dyskinesia and OFF time, were in favour of the 100 mg dose group.

Uncertainty in the knowledge about the beneficial effects

Apart from MAO-B inhibition, several other proposed mechanisms of action of safinamide, have been suggested by in-vitro data i.e. inhibition of dopamine and serotonin transporters, reduced stimulated release of glutamate without affecting basal glutamate levels, and reduction of the neuronal excitability by blocking voltage-gated sodium channels. The presented data did not allow for a clear conclusion on the extent to which the interaction with these pathways could contribute to the clinical effect of safinamide. Comparative studies with a 'pure' MAO-B inhibitor were lacking and no clinical effects that might be related to these mechanisms, such as a reduction in dyskinesia rating scores, were clearly evident in the clinical trials.

Safinamide as add-on therapy to a single DA-agonist in early stage non-fluctuating patients

The efficacy of safinamide was evaluated in three randomized placebo-controlled trials in patients with early Parkinson Disease without fluctuations, on a stable treatment with a dopamine-agonist. The primary outcome of these studies was an improvement in motor function from baseline, as compared to placebo, assessed by the UPDRS III scale. In the first study (009), a significant effect was shown in the short-term (at 12 weeks). However, this could not be confirmed by the longer-term pivotal confirmatory trials as the MOTION and Study 015 failed to meet the primary endpoints in their primary analyses (ITT, LOCF).

Post-hoc re-analyses were performed in a pooling exercise where data from the studies were analyzed together. This was not considered valid from a methodological point of view, as there were differences in duration and dose regimens of the pooled studies, and rendered the interpretation of the observed results

difficult. In addition to these methodological shortcomings, the observed outcomes in the primary endpoint were considerably smaller than those defined *a priori* as clinically relevant, and not consistently supported by a significant improvement in daily functioning, illustrating that the clinical relevance of the results was debatable. In the MOTION Study - considered as the most important one among the three studies available as this was by far the largest study, the treatment effect was marginal and sensitive to different data imputation methods.

Altogether the data presented in support of the indication in early PD patients has shown at best a marginal improvement of UPDRS motor scores, which was non-robust, and of questionable clinical relevance. The post-hoc analyses were not methodologically sound with regard to the pooling of data. Regarding the long-term effect of safinamide as add-on to a single DA-agonist in early PD patients safinamide did not significantly delay the time to the need for an increment of the background dopaminergic therapy.

Safinamide as add-on therapy to L-dopa alone or in combination with other PD medications in mid- to late-stage fluctuating patients

The inclusion of an active comparator would have helped to interpret the magnitude of the observed effect of increment of 30-60 minutes in ON-time in advanced PD patients, also considering that the treatment effect sizes on the primary endpoint showed considerable variability in the two trials. However, the committee concluded that the different point estimates of the pivotal studies fell within the variability seen in studies with add-on treatment with other MAO-inhibitors or dopamine-agonists in advanced PD patients, and were probably is due to differences in study populations. Although head-to-head studies with active comparators were lacking, the clinical relevance of the effect could be concluded upon from the favourable indirect comparison to other treatments with similar mode of action, used in this population.

Risks

Unfavourable effects

In general, safinamide was well tolerated in early stage PD patients.

Specific adverse events of interest

Retinal degeneration

Retinal degeneration was observed in studies in rats, which might have been due to accumulation of safinamide. Because of this risk, systematic ophthalmic monitoring was introduced in the trials, including routine testing of visual acuity, colour vision, peripheral field vision and fundoscopy, and Optical Coherence Tomography. Based on the data from the pre-clinical and clinical setting it could be concluded that treatment up to 2 years did not indicate an enhanced risk of ophthalmic events linked to the use of safinamide, as compared to placebo, in a group of 600 subjects. The ocular tomography measurements, which were considered as the most sensitive assay of the retina degeneration, did not indicate a trend of significant worsening thus far in a subgroup of 155 subjects with 1.5-2 years follow-up.

CNS risks

In the add-on setting to levodopa in late-stage PD patients, dyskinesias were twice as frequently reported at the use of safinamide than in placebo, however, they were rarely severe.

Frequently occurring neurological adverse events in both early stage PD and late stage PD patients were dizziness, headache, somnolence and tremor, at similar frequencies as reported under placebo treatment.

The most frequently observed psychiatric adverse events in both early stage PD and late stage PD patients were: insomnia, depression, anxiety and hallucination. Impulse control disorders and hypersexuality disorders occurred in less than 0.5% of patients.

Hepatotoxicity

Safinamide induced transaminase enzyme increments, though this was in general self-limiting, not associated with increments of bilirubin, AST or phosphatase. There were no cases of drug-induced liver toxicity.

Cardiovascular risks

Safinamide did not cause QTc prolongation in an active controlled study in healthy volunteers. Safinamide was not associated with cardiovascular risk in trials, though it is noted that a selected population at low risk was included.

Uncertainty in the knowledge about the unfavourable effects

Retinal degeneration

Based on the concern raised from the non-clinical setting, ophthalmic safety and retinal degeneration remain an important issue in future safety monitoring. A targeted questionnaire is to be developed, which will allow the collection of information from relevant events in the post-marketing setting in a more structured manner.

Special populations

There is limited experience in elderly patients, patients with severe renal and hepatic impairment, and patients with serious chronic cardiovascular disease. Data in very elderly will be generated post-marketing.

Furthermore, there is limited experience in patients at enhanced risk of retinal degeneration. As a precautionary measure, patients at risk of conditions such as (diabetic) retinopathy, uveitis, and hereditary retina disorders are excluded from the target population.

Co-medication

No relevant patterns in frequency or type of adverse events for the different co-medications including psychoactive drugs were observed in the trials. However, it is difficult to exclude interactions based on these observational data, as certain co-medications were infrequently used in the trials, and subjects were not stratified for the use of co-medications at inclusion.

Based on *in-vitro* data it cannot be excluded that safinamide is an inhibitor of BCRP in the small intestine and could potentially lead to DDIs. As the concentration of safinamide in the gastrointestinal tract exceeds the inhibition threshold only for a short period of time, an interaction is only expected with BCRP substrate with a tmax ≤ 2 hours, when safinamide and the substrate with a tmax of <2 hours are taken at the same time.

The potential for interaction of safinamide via CYP and P-gp is low, however the CHMP recommended that the company should still evaluate if safinamide may interact with BCRP substrates and submit the reports of several in vitro studies in which it should be investigated if safinamide affects the function of several transporters.

Safinamide is extensively metabolised into several inactive metabolites. The primary route of elimination is via unspecified amidases, which suggests a potential for DDI pharmacokinetic interactions. In this

context, the CHMP considered that the biotransformation of safinamide will be further investigated post-authorisation in an *in vitro* study on amidase enzymes, as reflected in the RMP.

Benefit-risk balance

Importance of favourable and unfavourable effects

There were no clearly demonstrated, clinically relevant benefits of safinamide applied as add-on therapy in the early stage Parkinson patients on a stable treatment with dopamine-agonists.

The most relevant favourable effect of safinamide was the improvement of 0.5-1 hrs in ON-time without troublesome dyskinesia, when the drug was administered as add-on treatment to levodopa therapy in mid-late stage Parkinson patients with motor fluctuations.

The most important adverse event is the higher risk of dyskinesia in advanced patients treated with levodopa, and the concern for a potential risk of retinal degeneration, as indicated by the non-clinical data in rats.

Benefit-risk balance

Discussion on the benefit-risk balance

Safinamide as add-on therapy to a single DA-agonist in early stage non-fluctuating patients

The benefits of safinamide in this setting, i.e. to non-fluctuating PD patients on a stable dose of a dopamine-agonist, were not robustly demonstrated. The treatment effects in the motor scores used as primary endpoints were below the targets that were pre-defined as clinically relevant in the protocol. Moreover, the observed changes were not consistently supported by a significant improvement in daily functioning, illustrating that the clinical relevance remained debatable. The use of safinamide did not significantly prevent a change in the dopaminergic background therapy in this setting. It remained unclear whether there are any criteria according to which patients that would benefit more from the treatment could be selected. The outcomes were not robust, and largely depended on how the assessed population was defined and on the methodology used to handle missing data.

The applicant argued that there was probably very little room for improvement by enhancing dopamine levels via MAO-B inhibition in patients that are stable on their dopamine agonist treatment. Although this may be a reasonable explanation for the disappointing results, it is still not sufficient to justify the use of safinamide in this setting.

During the assessment, the CHMP considered that the benefits of safinamide in the early PD setting were not robustly shown, and did not outweigh the risks. The Applicant did not pursue the indication in early PD any further during the marketing authorisation application procedure.

Safinamide as add-on therapy to L-dopa alone or in combination with other PD medications in mid- to late-stage fluctuating patients

Regarding the other pursued indication i.e. add-on to L-Dopa with/without additional anti-Parkinson medication, a statistically significant and clinically relevant effect was confirmed in both trials. The results with respect to secondary endpoints were consistent, and the positive effect was maintained in the long-term double-blind extension phase. The observed improvement of 0.5h or 1h in ON-time, respectively, was deemed clinically relevant in this population despite the lack of direct comparative data.

A clear beneficial effect on dyskinesia was not shown in the overall study population. One the one hand, this was expected as MAO-inhibition causes a dopaminergic effect, and this could result in dyskinesia. On

the other hand, based on the other postulated mechanisms of action (reduction of neuronal excitability by blocking voltage/gated sodium, reduced stimulated release of glutamate) it was anticipated that dyskinesia should have been controlled better. Nevertheless, the fact that no beneficial effect on dyskinesia was demonstrated did not negatively influence the benefit/risk balance.

Although an increased incidence of dyskinesia was noted, this is not necessarily a major issue considering that dyskinesias were usually mild and associated with an increase in ON-time. The overall incidence of troublesome dyskinesia was low and was not dose related.

Retinal degeneration had been observed in rats after safinamide-exposure. After the results of the rat study were known, extensive ophthalmological examinations were introduced in the safinamide development program. Systematic ophthalmological monitoring up to 2 years did not indicate retinal degeneration as a problem: There was no signal of worsening in retina and macula thickness at retinal tomography, and there were no differences in visual acuity, colour vision, peripheral vision or fundoscopy scores compared to placebo. The gathered evidence was reassuring, although this will remain an adverse event of special interest in future monitoring.

The overall benefit/risk balance of safinamide in the treatment of patients with idiopathic Parkinson's disease as add-on to a stable dose of L-dopa only or in combination with other PD medications in mid- to late-stage fluctuating patients was considered positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Xadago in the treatment of adult patients with idiopathic Parkinson's disease (PD) as add-on therapy to a stable dose of Levodopa (L-dopa) alone or in combination with other PD medicinal products in mid-to late-stage fluctuating patients is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to medical prescription

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation. Subsequently, the marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

These conditions fully reflect the advice received from the PRAC.

New Active Substance Status

Based on the CHMP review of data on the quality properties of the active substance, the CHMP considers that safinamide is qualified as a new active substance.