PRESS RELEASE

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On the World Parkinson's Day, Zambon announces Synapses study's results on Parkinson's patients in real special settings

The real-world Synapses study confirms the safety and tolerability of safinamide used as an adjunct therapy in patients with fluctuations mainly older, with comorbidities or psychiatric conditions.

On the occasion of the **World Parkinson's Day** occurred yesterday, Zambon officially presents results from its **SYNAPSES study** aimed at investigating the real-world use of safinamide in six European countries.

Safinamide is a multimodal drug with a dual mechanism of action, dopaminergic (reversible mono-amine oxidase-B inhibition) and non-dopaminergic (modulation of the abnormal glutamate release), **that offers an innovative approach to the management of motor and non-motor symptoms and motor complications**[1].

Study design

SYNAPSES (European multicenter retrospective-prospective cohort **S**tud**Y** to observe safi**NA**mide safety profile and pattern of use in clinical **P**ractice during the fir**S**t post-comm**E**rcialization pha**S**e) is a multinational, multicenter, retrospective/prospective cohort observational study, with 1,610 patients followed up to 12 months. The prospective observation was chosen because in most countries the study onset was expected to coincide with the drug commercialization, while the retrospective part was performed to include also patients starting treatment before the study onset.

The study was designed to include potentially all patients treated with safinamide as per clinical practice[2] and investigate the real-world use of safinamide in six European countries particularly in patients' populations not well represented in clinical trials such as **patients older than 75**, with **psychiatric illnesses** or with **relevant comorbidities**. Countries involved were Belgium, Germany, Italy, Spain, Switzerland and United Kingdom and the study was conducted in 128 neurology and geriatric centres, specialized in PD treatment[2].

Study primary and secondary objectives

Primary objective was to evaluate the occurrence of **adverse events in patients** treated with safinamide **in real-life conditions during 1 year** in the first post-commercialization phase as reported by the investigators, following an analysis conducted in the overall population, and in some subgroups of interest, namely in **patients aged under 75 years** and those **with relevant concomitant conditions**.

Secondary objectives included the description of the characteristics of patients treated with safinamide according to clinical practice and the description of safinamide treatment patterns in real-life setting as well as motor evaluations, as measured by UPDRS III (Unified Parkinson's Disease Rating Scale)[2].

Safety

During observation 45.8% patients experienced adverse events (AEs), 27.7% patients had adverse drug reactions and 9.2% patients had serious adverse events. The adverse events were those described in safinamide patients' information leaflet. **The majority of AEs were mild or moderate and completely resolved with no differences detected between the subgroup of patients** (i.e., older patients, with psychiatric conditions or relevant comorbidities). Clinically significant improvements were seen in the UPDRS motor score and in the UPDRS total score in ≥40% of patients[2]. The percentage of patients experiencing AEs during one year of treatment with safinamide in real-life conditions was **30% lower compared to the percentage observed in six-months pivotal trials**[3,4]. The monthly incidence rate of AEs was very low, 0.07 AEs per patient per month.

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[1] Müller T, Foley P (2017) Clinical pharmacokinetics and pharmacodynamics of safinamide. Clin Pharmacokinet 56, 251-261.

[2] G. Abruzzese et al. /Safinamide in Routine Clinical Practice.

[3] Borgohain R, Szasz J, Stanzione P, Meshram C, Bhatt M, Chirilineau D, Stocchi F, Lucini V, Giuliani R, Forrest E, Rice P, Anand R; Study 016 Investigators (2014) Randomized trial of safinamide add-on to levodopa in Parkinson's disease with motor fluctuations. Mov Disord 29, 229-237.

[4] Schapira AH, Fox SH, Hauser RA, Jankovic J, Jost WH, Kenney C, Kulisevsky J, Pahwa R, Poewe W, Anand R (2017) Assessment of safety and efficacy of safinamide as a levodopa adjunct in patients with Parkinson's disease and motor fluctuations. A randomized clinical trial. JAMA Neurol 74, 216-224.

Dyskinesia was the most frequently reported AE although it occurred in a lower frequency in the SYNAPSES study compared to previous pivotal trials (13.7% vs 18%)[2].

Prof. Giovanni Abbruzzese, DINOGMI, University of Genoa, Genova, Italy, said: *"This real-world setting study confirms the safety and tolerability of safinamide used as an adjunct therapy in patients with fluctuations and suggests that safinamide can be an effective and safe option even in subgroups of critical patients – older patients and patients with comorbidities or psychiatric conditions".*

Motor fluctuations

Safinamide was shown to **reduce of about 40–50% motor fluctuations with visible efficacy already at 4 months, in particular on wearing-off and early morning fluctuations**[2] which affect the majority of patients with PD. The pharmacological treatment of motor fluctuations is difficult and remain a real unmet need[5]. This significant and rapid-onset effect of safinamide may be explained by its dual mechanism of action, dopaminergic and glutamatergic. There is a significant association between motor fluctuations and annual costs of PD: the mean costs of patients with motor fluctuations are generally two-three times greater than the costs of patients without[6].

Prof. Alessandro Stefani, UOSD Parkinson, Università Policlinico Tor Vergata, Rome, affirmed: *"The majority of patients treated with levodopa experience motor fluctuations with a significant deterioration of their quality of life. The Synapses study showed that safinamide was able to reduce motor fluctuations and wearing-off, and as a consequence may improve subjects' QoL and hopefully reduce some of the economic burden of PD".*

The SYNAPSES study confirmed the safety and tolerability of safinamide, as adjunct therapy, in fluctuating patients and in special groups of subjects. Neither age, comorbidities, nor psychiatric conditions seem to have any relevant effect on its safety profile. Motor complications and motor scores improved with clinically significant results in the UPDRS scale maintained in the long-term. These results suggest that safinamide can be an effective and safe option for the management of motor fluctuations in levodopa-treated patients.

Paola Castellani, Global Chief Medical Officer and Patient's Access Head at Zambon, concluded: *"Listening to HCPs treating PD we learnt how much it is important to give physicians and patients a choice of treatment options, particularly in the area of PD where the needs of each patient are highly individual and should be precisely identified to manage both motor and non-motor symptoms. In Zambon we provide innovative treatment approaches to help bring under control different symptoms associated with PD and our aim is and always will be to support the scientific and medical community through studies, trainings, and scientific events, and to help people living with PD collaborating with their representative groups globally to better understand patient's unmet needs and increase their quality of life".*

Parkinson Disease and current treatments

Parkinson's disease (PD) is a neurodegenerative condition that affects nerve cells of the brain that control movement[7] . PD is the second most common neurodegenerative illness, currently affects approximatively 1.2 million people throughout Europe and this number is expected to double in the next 10 years[8]. It is a debilitating condition with a strong impact on the quality of life of patients and caregivers[1], being associated with motor symptoms, as resting tremor, bradykinesia, rigidity, and non-motor symptoms, as depression, apathy, sleep disorders, pain or gastrointestinal disturbances[9]. Current pharmacological management is largely based on symptomatic drugs. Traditional pharmacotherapies for PD aim to restore depleted dopamine levels in the brain but are limited by long-term complications, such as motor fluctuations and dyskinesia. Moreover, the existing medications usually do not alleviate non-motor symptoms[10]. Other neurotransmitters beyond dopamine, in particular glutamate, are believed to play important roles in the pathogenesis of primary symptoms, motor fluctuations, dyskinesia, and possibly neuronal cell loss[11]. Safinamide is a multimodal drug with a dual mechanism of action, dopaminergic (reversible mono-amine oxidase-B

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[5] Olanow CW, Watts RL, Koller WC (2001) An algorithm (decision tree) for the management of Parkinson's disease: Treatment guidelines. Neurology 56, S1–S86.

[6] Keränen T, Kaakkola S, Sotaniemi K, Laulumaa V, Haapaniemi T, Jolma T, Kola H, Ylikoski A, Satomaa O, Kovanen J, Taimela E, Haapaniemi H, Turunen H, Takala A (2003) Economic burden and quality of life impairment increase with severity of PD. Parkinsonism Rel Disord 9, 163-168.

[7] www.parkinson.it/morbo-di-parkinson.html

[8] de Lau LM, Giesbergen PC, de Rijk MC, Hofman A, Koudstaal PJ, BretelerMM (2004) Incidence of parkinsonism and Parkinson's Disease in a general population: The Rotterdam Study. Neurology 63, 1240-1244.

[9] Chaudhuri KR, ShapiraAH (2009) Non-motor symptoms of Parkinson's disease: Dopaminergic pathopshysiology and treatment. Lancet Neurol 8, 464-474.

[10] Hauser RA (2009) Levodopa: Past, present and future. Eur Neurol 62, 1-8.

[11] Chase TN, Bibbiani F, Oh JD (2003) Striatal glutamatergic mechanisms and extrapyramidal movement disorders. Neurotox Res 5, 139-146.

inhibition) and non-dopaminergic (modulation of the abnormal glutamate release), that offers an **innovative approach to the management of motor and non-motor symptoms and motor complications**.[1]

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