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<b>Population Pharmacokinetics of Safinamide and its Effect on Disease Progression in Parkinson's Disease</b> M. Campioni (1), S. Krösser (1), M.M. Thapar (2)*, S.C. Hayes (2), E. Gibiansky (3), V. Lucini (4), R. Anand (5), *Presenting author (1)Merck Serono SA, Geneva, Switzerland; (2) ICON Development Solutions, Marlow, Buckinghamshire, UK; (3) QuantPharm LLC, N.Potomac, Maryland, USA, (4) Newron Pharmaceuticals, SpA, Bresso, Italy, (5) APC, AG, St Moritz, Switzerland	
<a href="#">Mita Thapar</a>	
Poster: Applications- CNS	
<b>Background:</b> Safinamide (SAF), a first-in-class agent in Parkinson's disease (PD), is an $\alpha$ -aminoamide derivative with dopaminergic and non-dopaminergic mechanisms of action in development as an add-on therapy to a dopamine agonist or l-dopa.	
<b>Objectives:</b> To describe the population pharmacokinetics (PPK) of SAF and its effect on clinical endpoint (ON-time including minor dyskinesia) to develop a disease progression (DP) model.	
<b>Methods:</b> The PPK model was developed using concentration-time data from two Phase 3 studies:	
<ol style="list-style-type: none"> <li>1. 177 PD patients on a single dopamine agonist and 50-200mg/day of SAF (1099 SAF concentrations)</li> <li>2. 446 PD patients with motor fluctuations on stable l-dopa dose and 50 or 100mg/day of SAF (1620 SAF concentrations).</li> </ol>	
The DP model was based on ON-time values from 668 patients in Study 2 (SAF or placebo arms; 3603 ON-time scores). ON-time was modelled as a linear function of time with baseline ON-time, intercept (INT; effect with onset before the 1st post-dose visit at 4 weeks) and slope (SLOP) parameters, modelling the effect of steady-state SAF exposure/dose as covariate. The tested covariates were weight, age, gender, creatinine clearance, (change in) l-dopa dose and SAF exposure. Nonlinear mixed-effects modelling with NONMEM 6.2 (FOCEI method) was used. Final models were evaluated using predictive check simulations (VPC and PC-VPC) and bootstrap analysis.	
<b>Results:</b> PPK: A linear 1 compartment model with 1st order absorption described the data well. CL/F, Vd/F and KA (95% CI) were 4.96 (4.73-5.21) L/h, 166 (158-174) L and 0.582 (0.335-0.829) h <sup>-1</sup> , respectively, all estimated with good precision (RSE <22%). CL/F and Vd/F were allometrically related to weight (power 0.75 and 1, respectively). The inter-individual variability (IIV) was low (<30%).	
DP: INT was 0.73 (0.51-0.94) h for SAF, 0 for placebo; SLOP was 0.117 (0.078-0.156) h/month, non differentiable between SAF and placebo. RSE was low (<17%). IIV was 304% for SLOP and 249% for INT. Refined modelling using SAF exposure as covariate on INT and SLOP was unsuccessful.	
<b>Conclusions:</b> The models adequately describe the PPK of SAF and its effect on ON-time. SAF resulted in a typical ON-time increase of 0.73 h. High IIV in the model parameters and the limited duration of the study (in relation to persistence of placebo effect) prevented differentiation of the various SAF doses with respect to ON-time. Age, gender, renal function and l-dopa dose did not influence the PK and pharmacodynamics of SAF, suggesting dose adjustments are not required in a broad population.	

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