Populations pharmacokinetics and pharmacokinetic-pharmacodynamic correlations of tideglusib for the treatment of adolescents with autism spectrum disorders (ASD)

Alessandro Di Deo¹, Sean Oosterholt², Joseph Horrigan², Alison McMorn², Oscar Della Pasqua¹

¹ Clinical Pharmacology & Therapeutics Group, University College London, UK, ² AMO Pharma Ltd, Godalming, Surrey, UK

INTRODUCTION

Tideglusib is a glycogen synthase kinase 3β (GSK-3β) inhibitor. Dysregulation of translation of preclinical data, the dose rationale in humans is fraught with the behaviour, interests, or activities [5]. In addition to the uncertainties in the social communication and interaction, and restricted, repetitive patterns of behaviour forms the basis of diagnosis, with criteria focused on impairment in psychiatric disorders [1]. Recently, tideglusib has been proposed as a potential therapeutic target for the treatment of ASDs. ASDs are complex, pervasive, and integrated modelling approach based on Bayesian principles can be successfully used to mitigate these limitations. The objective of this investigation was to characterise the PK of tideglusib in adolescents with ASD following treatment over a period of 12 weeks and explore the correlation between exposure and core measures of efficacy.

METHODOLOGY

Initially, concentration data from Phase I studies in healthy adult and elderly subjects (n=54) were used to investigate the population PK of tideglusib and explore the role of relevant factors affecting systemic exposure. Model parameter distributions were subsequently used as priors for the evaluation of sparse PK data in adolescents affected by ASD (n=38). Data analysis was performed using a nonlinear mixed effects approach. Finally, linear regression techniques were used to assess the statistical significance of the correlation between model-predicted estimates of exposure (e.g., AUC, Cmax, cumulative AUC, Css) and core measures of efficacy (e.g., Repetitive Behaviour Scale - Revised, Vineland Adaptive Behavior Scales – II and Aberrant Behaviour Checklist), as determined by linear interpolation of the area under the effect curve (AUEC) during treatment and the change in scores at predefined visit days relative to baseline.

CONCLUSION

• Implementation of an integrated modelling approach based on Bayesian principles can be successfully used to mitigate the paucity of PK and PD data in rare diseases, enabling the evaluation of the effect of covariate factors on pharmacokinetics, and more specifically on systemic exposure.

• Evidence of a correlation between drug exposure and changes in core measures of efficacy in adolescents with ASD represent an initial step in the evaluation of the efficacy of tideglusib.

• The observed clinical improvement in subscales (domains) can be assigned to the beneficial effects of tideglusib. These results also suggest that there may be selectivity of action. Endpoints that describe impairing behaviours associated with ASD should be prioritised in future clinical trials.