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

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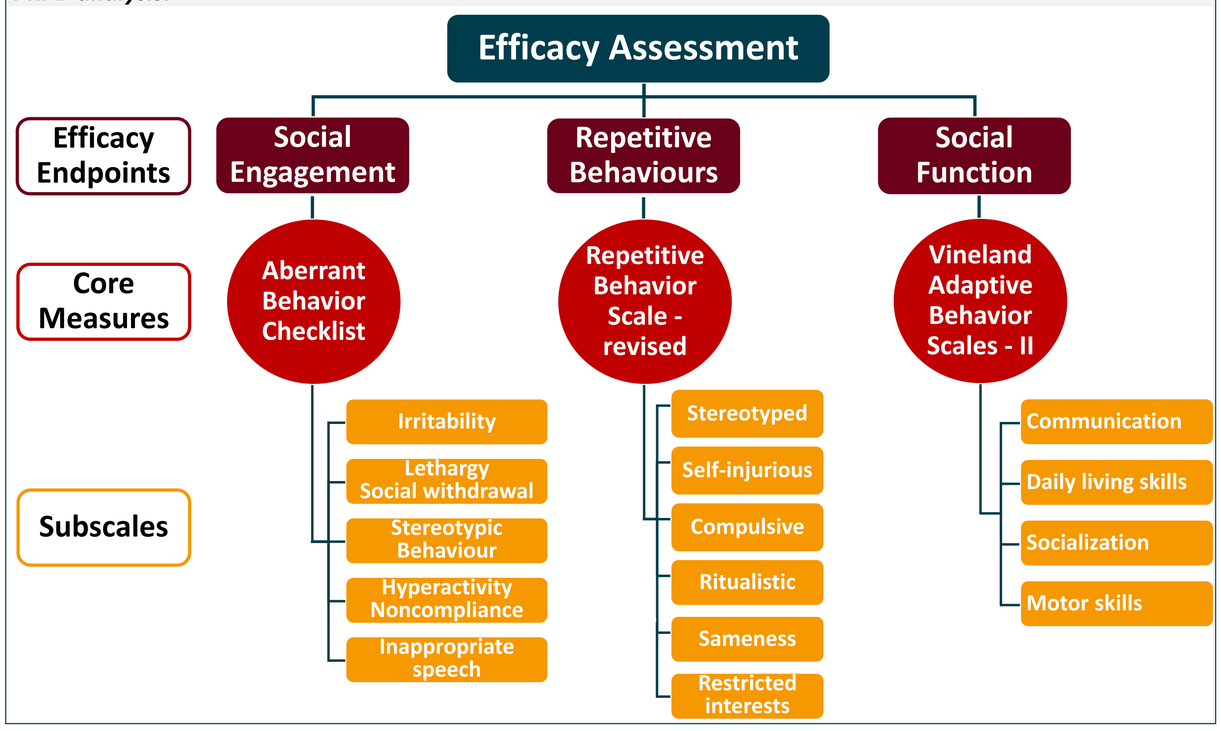
INTRODUCTION

Tideglusib is a glycogen synthase kinase 3ß (GSK-3ß) inhibitor. Dysregulation of signalling pathways involving GSK-3 is associated with several neurological and psychiatric disorders [1]. Recently, tideglusib has been proposed as a potential therapeutic agent for the treatment of ASDs. ASDs are complex, pervasive, and multifactorial neurodevelopmental conditions [2-4]. Observation of aberrant behaviour forms the basis of diagnosis, with criteria focused on impairment in social communication and interaction, and restricted, repetitive patterns of behaviour, interests, or activities [5]. In addition to the uncertainties in the translation of preclinical data, the dose rationale in humans is fraught with the paucity of pharmacokinetic (PK) and pharmacodynamic (PD) data available for subsequent evaluation of efficacy in Phase II-III studies. Implementation of an 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, C_{max}, cumulative AUC, C_{ss}) 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.

Figure 1. Schematic diagram of the core measures of efficacy and corresponding subscales available for the PKPD analysis.



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.

References

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4. Simonoff E et al. Psychiatric disorders in children with autism spectrum disorders: prevalence, comorbidity, and associated factors in a population-derived sample. J Am Acad Child Adolesc Psychiatry. 2008; 47(8):921-929.
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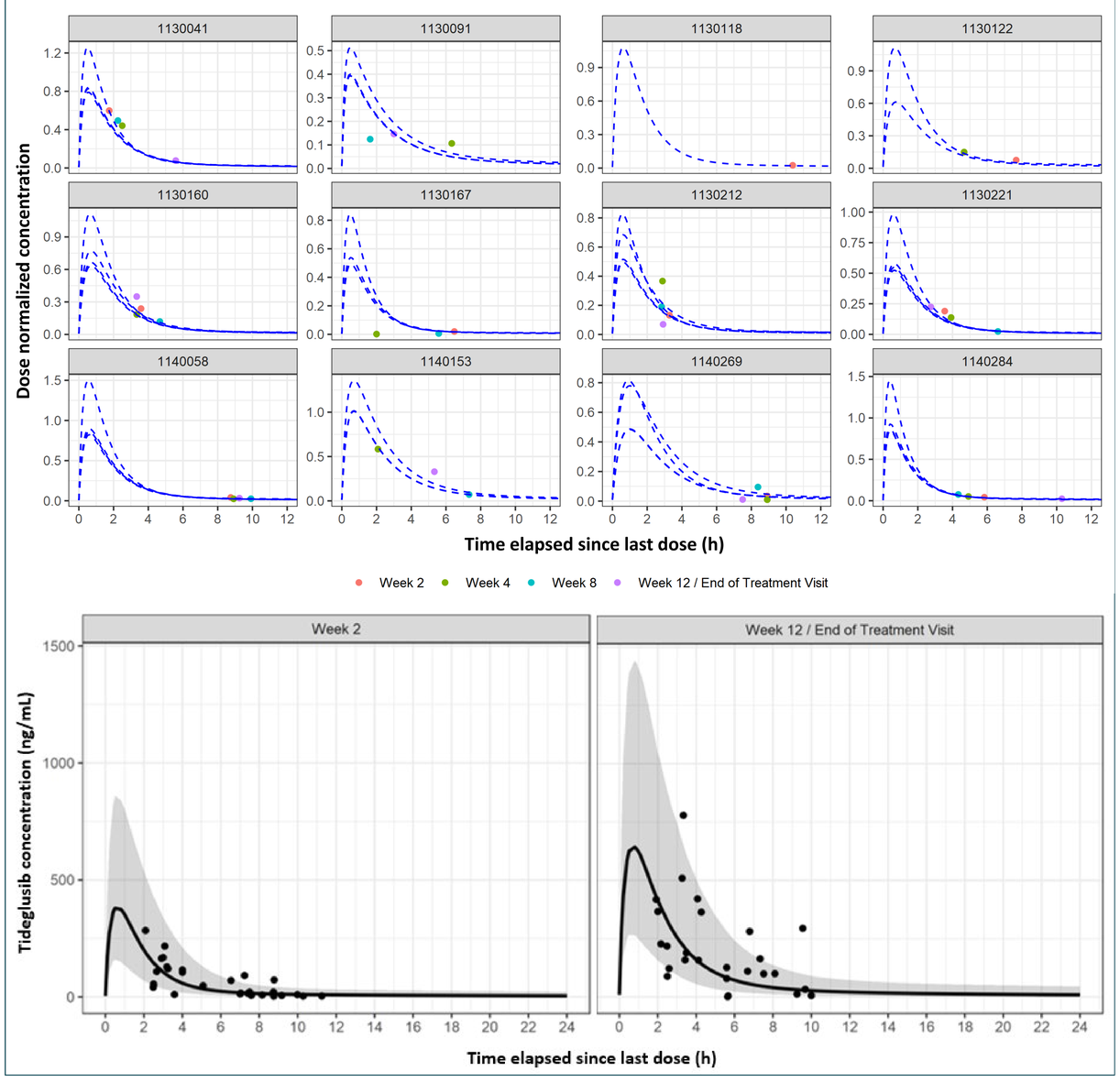
Pharmacokinetics

Tideglusib exposure in adolescent patients (12-17 years old) suffering from ASD was adequately described by a 2-compartment PK model. Dose (strength) was found to have a statistically significant effect on residual variability in this population, with different parameter estimates for doses higher than 400 mg. IIV was identified for all PK parameters (i.e., CL, V1, V2,Q and KA).

Figure 2. Upper panels show the predicted concentration vs. time profiles in adolescent. Solid circles are observed concentrations stratified by visit. Red and blue dashed lines indicate the individual and population predicted concentrations, respectively.
Lower panels depict the visual predictive checks for the final PK model. Solid line represents the median profile, whilst the shaded area indicates the 90%-confidence interval of simulated values. Dots are the observed data.



PKPD CORRELATION

Exploratory analysis of the correlations between tideglusib exposure and core efficacy measures showed that changes from baseline were significantly correlated with tideglusib AUC. Briefly, despite large heterogeneity in the population, clinically and statistically significant improvement was observed in Repetitive Behaviours (mainly Ritualistic Behavior and Restricted interests Behavior).

Figure 3. Correlation between AUC and change from baseline in RBS Revised (Ritualistic Behavior - Total Subscale Score). Individual observations are represented by dots; each individuals is shown with a different colour. Results are presented for different treatment intervals in separate panels.

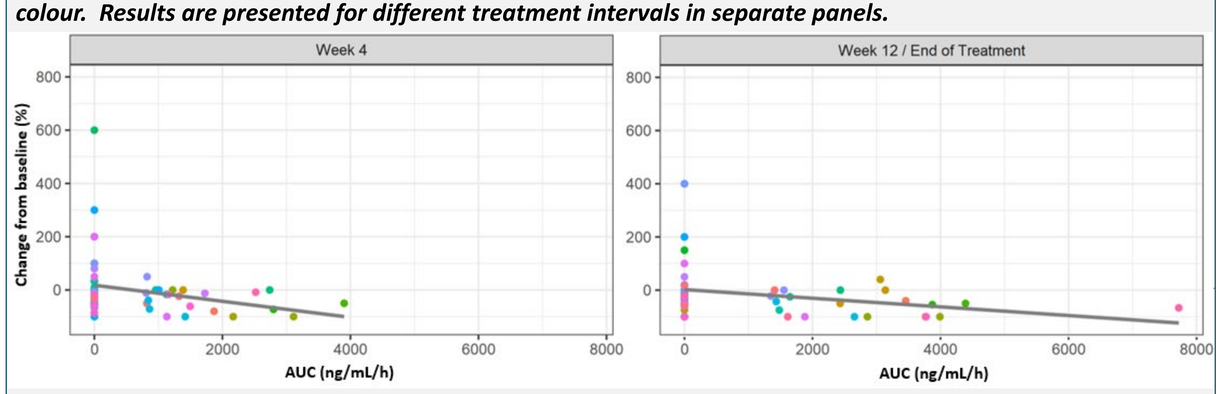
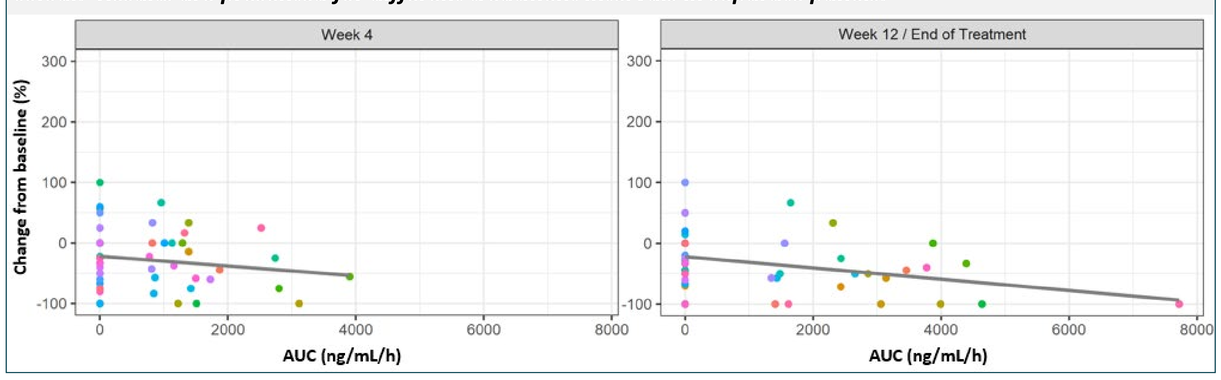


Figure 4. Correlation between AUC and change from baseline in RBS Revised (Restricted Behavior - Total Subscale Score). Individual observations are represented by dots; each individuals is shown with a different colour. Results are presented for different treatment intervals in separate panels.



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