In Silico Physiologically Based Pharmacokinetic Model of the Effect of Hepatic Impairment on Trofinetide Exposures

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BACKGROUND

- Trofinetide, a synthetic analog of the naturally occurring brain tripeptide glycine-proline-glutamate, is the first US Food and Drug Administration–approved treatment for Rett syndrome (RTT)[1]
- RTT is a rare, X-linked neurodevelopmental disorder caused primarily by loss-of-function mutations in the *MECP2* gene[2] and manifests in early infancy, when signs of neurological dysfunction and developmental regression are observed[3,4]
- The condition mainly affects females, occurring in approximately 1 in 10,000 to 1 in 15,000 female births worldwide[5,6]
- Although neurological symptoms predominate, RTT is associated with multisystem comorbidities, including metabolic, hepatic, and gastrointestinal disorders[7–9]
- Trofinetide is orally administered and is excreted predominantly via the renal route,[10] so it is not anticipated that hepatic impairment would modify its pharmacokinetic profile; nevertheless, understanding the pharmacokinetics of trofinetide in individuals with hepatic impairment is of clinical interest to manage dosing in cases of RTT associated with hepatic comorbidity

OBJECTIVE

- To compare estimates of trofinetide exposure in virtual healthy subjects and virtual patients with varying degrees of hepatic impairment using physiologically based pharmacokinetic (PBPK) modeling

METHODS

Trofinetide PBPK Model

- Simulation of trofinetide exposure was performed using a validated PBPK model (unpublished) in conjunction with GastroPlus® v9.8 and PBPKPlus™ software (Simulations Plus, Lancaster, CA); compilation and processing of PBPK model outputs were performed with Microsoft Excel and R software v3.4.3 (Foundation for Statistical Computing, Vienna, Austria)
  - The PBPK model incorporated physicochemical data for trofinetide and information (obtained experimentally or optimized during model development) on its absorption, distribution, and elimination
  - Physiological model parameters (including volumes, blood flow, organ weights, and hematocrit values) were generated using the PEAR Physiology™ module of PBPKPlus™
- Trofinetide dosing was simulated for healthy adult physiologies and physiologies representing mild, moderate, and severe hepatic impairment (Child-Pugh Classes A, B, and C, respectively); since hepatic impairment is frequently associated with renal impairment,[11] the built-in physiologies incorporated both effects
- To evaluate the impact of hepatic impairment alone, renal function was adjusted to match that of the healthy adult subjects (controls)
- The model-predicted pharmacokinetic profile for trofinetide was validated against data from clinical studies of orally and intravenously administered trofinetide

PBPK Model Simulations

- Deterministic simulations to estimate trofinetide exposure (maximum observed concentration [C_{max}] and area under the concentration-time curve from time 0 to infinity [AUC_{inf}]), obtained with a single oral dose of 12 g (based on the maximum recommended therapeutic dosage of 12 g twice daily), were performed in virtual patients with mild, moderate, and severe hepatic impairment (1 patient per category) and in virtual healthy controls matched for age, body weight, sex, and glomerular filtration rate
- Population (stochastic) simulations, based on random sampling of physiological input parameters, were performed to assess the potential interindividual variability in trofinetide pharmacokinetics following administration of an oral dose of 12 g among patients with hepatic impairment
- Trofinetide exposures were presented for both plasma and blood using a conversion formula to account for the effects of alterations in hematocrit on the trofinetide blood:plasma concentration ratio:

$$Rbp_{adj} = \frac{Hct_{adj}}{0.45} \times (Rbp_{adult} - [1 - 0.45]) + (1 - Hct_{adj})$$

Rbp_{adj} = adjusted blood:plasma concentration ratio in defined hepatic impairment population
Rbp_{adult} = blood:plasma concentration ratio in healthy adults (0.525, based on clinical data)
Hct_{adj} = hematocrit in defined hepatic impairment population
0.45 = hematocrit in healthy adults

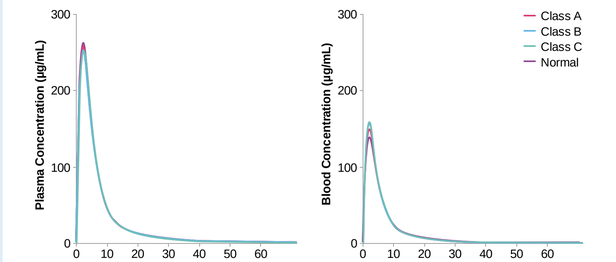
- Bioequivalence between hepatic impairment and healthy control populations was assessed through analysis of variance of log-transformed C_{max} and AUC_{inf} values from stochastic simulations; bioequivalence was assumed if the 90% confidence interval of the geometric mean ratio of the log-transformed values fell within the limits of 0.80 and 1.25

RESULTS

Deterministic Simulations of Hepatic Impairment

- Predicted plasma trofinetide exposures (C_{max} and AUC_{inf}) were similar for the virtual healthy controls and the individual virtual patients with mild, moderate, and severe hepatic impairment (**Figure 1**)

Figure 1. Deterministic simulation of trofinetide plasma and blood exposures in virtual healthy controls and in individual virtual patients with hepatic impairment receiving a single oral dose of trofinetide 12 g



Class A, Class B, and Class C refer to the Child-Pugh classifications of varying degrees of hepatic impairment (mild, moderate, and severe, respectively); normal represents the age and body weight–matched healthy controls

- On conversion of plasma concentrations to blood concentrations, both C_{max} and AUC_{inf} increased as the severity of hepatic impairment increased, reflecting the impact of the lower hematocrit values assigned to the patients with mild, moderate, and severe hepatic impairment (0.40, 0.36, and 0.35, respectively) compared with the healthy controls (0.45)

Stochastic Simulations of Hepatic Impairment

- For each of the 4 study populations (healthy controls and mild, moderate, and severe hepatic impairment), 100 virtual individuals were created
  - The populations were well matched for age, body weight, height, and glomerular filtration rate (**Table 1**)
- Varying ranges of hematocrit and trofinetide blood:plasma concentration ratios were predicted across the 4 populations: increases in the severity of hepatic impairment were associated with progressive reduction in hematocrit and elevation of the trofinetide blood:plasma concentration ratio
- Consistent with the deterministic simulations, predicted plasma exposures (C_{max} and AUC_{inf}) based on the stochastic simulations were similar for healthy controls and patients with mild, moderate, and severe hepatic impairment (**Table 2**, **Figure 2A**)
- In line with the reduction in hematocrit values associated with hepatic dysfunction, the predicted trofinetide blood:plasma concentration ratio increased as the severity of hepatic impairment increased (**Table 1**)
- As a consequence, blood trofinetide exposure (C_{max} and AUC_{inf}) increased slightly as the severity of hepatic impairment increased (mean C_{max}: 130.8 µg/mL [healthy controls] vs 148.5 µg/mL [Class A] vs 154.6 µg/mL [Class C]) (**Table 2**, **Figure 2B**)

Table 1. Demographic and physiological characteristics of virtual populations of healthy controls and patients with hepatic impairment generated via PBPK-modeled stochastic simulations

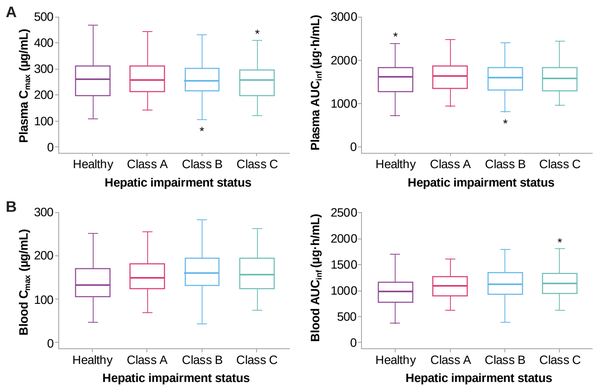
Population characteristic	Healthy controls (N = 100)	Patients with hepatic impairment (Child-Pugh classification)		
		Class A (N = 100)	Class B (N = 100)	Class C (N = 100)
Age, years, mean (range)	64.6 (55–75)	64.4 (55–75)	64.6 (55–75)	65.1 (55–75)
Body weight, kg, mean (range)	84.3 (72.6–102.2)	85.9 (72.8–101.3)	84.7 (72.5–102.1)	85.7 (73.1–101.8)
Height, cm, mean (range)	168.0 (151.8–183.7)	169.6 (151.3–187.9)	167.3 (151.1–184.6)	167.6 (151.0–187.5)
Female sex, n	44	45	49	49
Glomerular filtration rate, mL/min, mean (range)	95.1 (59.9–132.1)	95.1 (63.0–138.8)	95.1 (65.3–135.4)	95.1 (63.3–147.6)
Hematocrit, mean (range)	0.44 (0.35–0.57)	0.40 (0.32–0.50)	0.36 (0.29–0.45)	0.35 (0.29–0.45)
Trofinetide blood:plasma concentration ratio, mean (range)	0.53 (0.32–0.67)	0.58 (0.42–0.72)	0.63 (0.46–0.78)	0.63 (0.53–0.72)

Table 2. Stochastic simulations of trofinetide exposure following a single oral dose of trofinetide 12 g in virtual populations of healthy controls and patients with hepatic impairment

Parameter	Healthy controls (N = 100)	Patients with hepatic impairment (Child-Pugh classification)		
		Class A (N = 100)	Class B (N = 100)	Class C (N = 100)
Plasma C_{max}, µg/mL, mean (%CV)	247.6 (33.5)	258.0 (25.9)	245.7 (34.6)	244.8 (29.3)
Plasma AUC_{inf}, µg·h/mL, mean (%CV)	1804 (26.9)	1862 (21.9)	1762 (28.8)	1789 (24.3)
Blood C_{max}, µg/mL, mean (%CV)	130.8 (37.2)	148.5 (27.5)	153.4 (35.9)	154.6 (29.5)
Blood AUC_{inf}, µg·h/mL, mean (%CV)	953.1 (31.7)	1072 (23.8)	1101 (30.8)	1130 (25.5)

%CV, coefficient of variation expressed as a percentage; AUC_{inf}, area under the concentration-time curve from time 0 to infinity; C_{max}, maximum observed concentration

Figure 2. Box plots of predicted trofinetide plasma (A) and blood (B) exposures following a single oral dose of trofinetide 12 g in virtual populations of healthy controls and patients with hepatic impairment



Boxes represent the 25th and 75th percentiles, and lines represent the median
Whiskers extend to the most extreme values within the 1.5-interquartile range; values outside the range are indicated by asterisks
AUC_{inf}, area under the concentration-time curve from time 0 to infinity; C_{max}, maximum observed concentration

Bioequivalence Determinations

- Bioequivalence in terms of plasma exposures was demonstrated between healthy controls and patients with hepatic impairment receiving a single oral dose of trofinetide 12 g (**Table 3**)
- For the populations with moderate and severe hepatic impairment, the upper 90% confidence interval values for C_{max} in whole blood fell marginally outside the defined limit for bioequivalence (**Table 3**)
  - These excursions from bioequivalence were not clinically relevant, amounting to 0.004 units (moderate hepatic impairment) and 0.001 units (severe hepatic impairment) in excess of the limit of 1.25 units

Table 3. Bioequivalence assessment with plasma and blood data sets

Comparison	Geometric mean ratio (90% confidence interval)	
	C_{max}	AUC_{inf}
Plasma		
Class A vs controls	1.042 (0.985, 1.103)[a]	1.032 (0.983, 1.084)[a]
Class B vs controls	0.992 (0.933, 1.055)[a]	0.977 (0.931, 1.026)[a]
Class C vs controls	0.989 (0.937, 1.043)[a]	0.992 (0.949, 1.038)[a]
Blood		
Class A vs controls	1.135 (1.067, 1.208)[a]	1.125 (1.063, 1.189)[a]
Class B vs controls	1.173 (1.097, 1.254)	1.155 (1.093, 1.221)[a]
Class C vs controls	1.182 (1.117, 1.251)	1.186 (1.128, 1.248)[a]

[a]Meets the bioequivalence acceptance criteria: the 90% confidence interval value falls within the range of 0.80 to 1.25
AUC_{inf}, area under the concentration-time curve from time 0 to infinity; C_{max}, maximum observed concentration

CONCLUSIONS

- Trofinetide plasma exposure in patients with mild, moderate, or severe hepatic impairment is bioequivalent to that in healthy controls
- Hepatic impairment is not anticipated to have a clinically relevant effect on trofinetide exposure in plasma or blood
- Differences between predicted plasma and blood concentrations of trofinetide are due to hematocrit adjustment

REFERENCES

1. Keam SJ. *Drugs*. 2023;83:819–824.
2. Bedogni F, et al. *Cereb Cortex*. 2016;26:2517–2529.
3. Hagberg B. *Ment Retard Dev Disabil Res Rev*. 2002;8:61–65.
4. Pini G, et al. *Orphanet J Rare Dis*. 2016;11:132.
5. Kirby RS, et al. *J Pediatr*. 2010;156:135–138.e1.
6. Hagberg B. *Acta Paediatr Scand*. 1985;74:405–408.
7. Fu C, et al. *BMJ Paediatr Open*. 2020;4:e000731.
8. Kyle SM, et al. *Open Biol*. 2018;8:170216.
9. Motil KJ, et al. *J Pediatr Gastroenterol Nutr*. 2019;68:799–805.
10. Darwish M, et al. *Clin Drug Investig*. 2022;42:513–524.
11. Johnson TN, et al. *Clin Pharmacokinet*. 2010;49:189–206.

ACKNOWLEDGMENTS

The study was supported by Acadia Pharmaceuticals Inc. (San Diego, CA, USA). Medical writing support was provided by Andrew Fitton, PhD, on behalf of Evidence Scientific Solutions, Inc., and funded by Acadia Pharmaceuticals Inc.

DISCLOSURES

MD, **JMY**, and **HB** are employees and stakeholders of Acadia Pharmaceuticals Inc. **ONO** and **ID** are employees of and hold stock in Cognigen Corporation (a Simulations Plus company). **VL** is an employee of and holds stock in Simulations Plus, Inc.

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Presented at the American College of Clinical Pharmacology (ACCP) Annual Meeting, September 10–12, 2023, Bellevue, WA, USA

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