Limited Potential for Interactions Between Trofinetide, a New Treatment for Rett Syndrome, and Drugs Metabolized by CYP3A4

Mona Darwish,[1] James M. Youakim,[1] Inger Darling,[2] Viera Lukacova,[3] Joel S. Owen,[2] Heather Bradley,[1] Kathie Bishop[1]

[1]Acadia Pharmaceuticals Inc., San Diego, CA, USA; [2]Cognigen Corporation (a Simulations Plus company), Buffalo, NY, USA; [3]Simulations Plus, Inc., Lancaster, CA, USA

BACKGROUND

- Trofinetide, a synthetic analog of glycine-proline-glutamate, was recently approved for the treatment of Rett syndrome (RTT) based on the results of the 12-week, randomized, placebo-controlled, phase 3 LAVENDER study (NCT04181723)[1,2]
- Almost 9 of 10 individuals with RTT have seizures during their lifetime,[3,4] with the majority requiring antiseizure medication at some point
- Cytochrome P450 3A4 (CYP3A4) is responsible for the metabolism of more than 50% of therapeutic drugs[5,6] (including several anti-convulsant drugs used in the treatment of seizures in RTT)[7] and is the most highly expressed cytochrome P450 isoenzyme in the liver and intestines[8–11]
- In vitro studies suggest that trofinetide has low potential to inhibit CYP3A4 in the liver at targeted systemic concentrations but could potentially inhibit CYP3A4 in the gut due to higher trofinetide concentrations that may be present locally after oral dosing

OBJECTIVE

- The objective of this study was to determine the effect of oral trofinetide on the pharmacokinetics (PK) of coadministered midazolam, a sensitive index substrate for CYP3A4, using a physiologically based pharmacokinetic (PBPK) model
  - Simulations of oral versus intravenous (IV) midazolam were assessed to differentiate potential effects of trofinetide on local (gut) and systemic (liver) metabolism via CYP3A4

METHODS

Development of the Trofinetide PBPK Model

- GastroPlus® 9.8 (Simulations Plus, Lancaster, CA) and its associated modules (PBPKPlus™, Advanced Compartmental Absorption and Transit [ACAT™], and Population Estimates for Age-Related Physiology [PEAR Physiology™]) were used to perform the PBPK simulations
- The PBPK model incorporated physicochemical properties of trofinetide and information on absorption, dissolution, and elimination, which were determined experimentally or optimized during model development
  - Dissolution and absorption were described using the ACAT module
  - Physiological model parameters (volumes, blood flow, organ weights) were generated using the PEAR Physiology module within PBPKPlus
  - Renal elimination was defined by glomerular filtration rate multiplied by the fraction of unbound drug in the plasma
- The following assumptions were applied to the model:
  - Trofinetide is absorbed from the gut via a passive diffusion process
  - Elimination in urine occurs via passive renal filtration, with no measurable amount of metabolism
  - A trofinetide blood-to-plasma concentration ratio of 0.525 was assumed for healthy adult subjects based on preclinical findings
- The predicted PK profile for trofinetide was validated using data from clinical studies for which full profile PK data were available after oral or IV trofinetide administration

Drug-Drug Interaction (DDI) Assessment

- A previously developed PBPK model for midazolam was included in the GastroPlus standards database and used for the analysis
- Using the DDI module in GastroPlus, deterministic simulations were performed using a healthy male physiology (30 years of age, 70 kg) to assess midazolam exposure parameters (maximum observed concentration [C_{max}] and area under the concentration-time curve from time 0 to infinity [AUC_{inf}]) for oral (15 mg) or IV (2 mg) midazolam with and without coadministration of oral trofinetide at the anticipated therapeutic dose (12 g)
- To determine potential variability in the DDI, a series of stochastic (population) simulations were performed in 100 virtual healthy subjects using a crossover study design between single 15-mg oral midazolam administration alone and in combination with 12 g trofinetide (both drugs administered at time 0)
- The assumption that trofinetide at a concentration of 15 mM inhibits 50% of CYP3A4 activity (IC_{50}) was applied to the model
- The geometric mean ratios of the C_{max} and AUC_{inf} for midazolam from the simulations ([trofinetide + midazolam] / midazolam [reference or baseline]) are presented, along with the corresponding 90% confidence intervals, as a measure of the DDI; the geometric mean ratios indicate the change in exposure to midazolam (or magnitude of CYP3A4 inhibition) by trofinetide

RESULTS

Deterministic Simulations of DDI

- The C_{max} and AUC_{inf} for midazolam were increased by 18% and 30%, respectively, when the 15-mg oral dose was coadministered with oral trofinetide (12 g) (**Table 1**)
  - The terminal slopes of the midazolam concentration-time profiles with and without trofinetide coadministration were parallel, suggesting trofinetide had no impact on the systemic clearance of midazolam (**Figure 1**)
- The fraction of oral dose reaching the portal vein (FDp) and bioavailability (F) for midazolam increased by 30% with coadministration of trofinetide, suggesting inhibition of midazolam metabolism in the intestines but no effect on first-pass extraction from the liver (**Table 1**)

Table 1. Model-predicted midazolam plasma exposures after 15-mg single oral midazolam dose or 2-mg IV midazolam dose administration with and without CYP3A4 inhibition by trofinetide

Route of midazolam administration and parameter	Midazolam PK parameter		Predicted ratio (DDI/baseline)
	No trofinetide (baseline)	With trofinetide (DDI)	
Oral[a] (15 mg)			
Fa (%)	99.99	99.99	1.000
FDp (%)	44.95	58.41	1.299
F (%)	24.87	32.33	1.300
Plasma C_{max} (µg/mL)	0.071	0.084	1.183
Plasma AUC_{inf} (ng × h/mL)	179.8	233.9	1.301
IV[b] (2 mg)			
FDp (%)	NA	NA	NA
F (%)	NA	NA	NA
Plasma C_{max} (µg/mL)	0.093	0.093	1.001
Plasma AUC_{inf} (ng × h/mL)	96.15	96.24	1.001

[a]Oral midazolam was administered concurrently with oral trofinetide; [b]IV midazolam was administered 2 hours after oral trofinetide

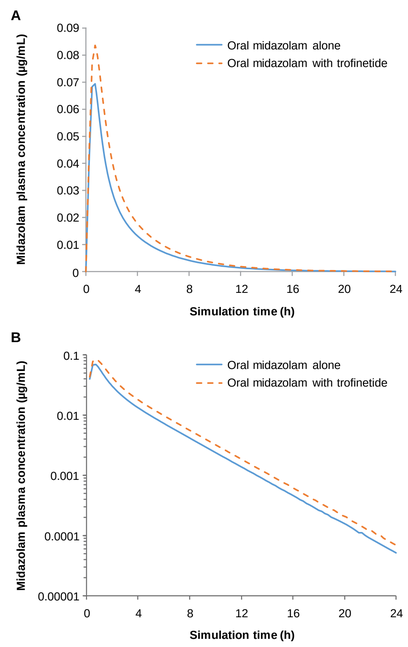
AUC_{inf}, area under the concentration-time curve from time 0 to infinity; C_{max}, maximum observed concentration; CYP3A4, cytochrome P450 3A4; DDI, drug-drug interaction; F, bioavailability; Fa, fraction absorbed; FDp, fraction of oral dose reaching the portal vein; h, hours; IV, intravenous; NA, not applicable; PK, pharmacokinetic

- The trofinetide concentration exceeded the IC_{50} for CYP3A4 in the duodenum (C_{max} = 25.5 mg/mL [80.9 mM] after 0.3 hours) and upper jejunum (C_{max} = 8.35 mg/mL [26.5 mM] after 0.7 hours) but declined below the IC_{50} within 2 hours of oral dosing (**Figure 2**)
- When IV midazolam was administered 2 hours after oral trofinetide, the predicted midazolam plasma concentration profiles were identical to those when IV midazolam was administered alone (**Figure 3**, **Table 1**)

Predicted Variability of the DDI (Stochastic Simulations)

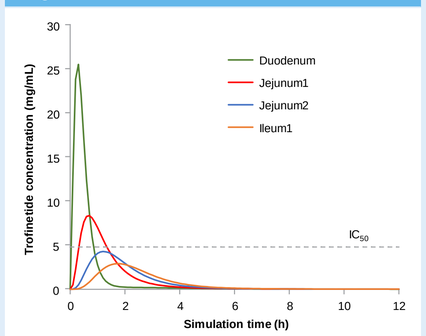
- The crossover assessment, which compared the predicted baseline (no trofinetide) and DDI (with trofinetide) plasma concentrations for midazolam in each virtual subject, showed a slight increase in the midazolam plasma concentration profile following trofinetide coadministration (**Figure 4**)
  - PK parameters increased by a similar magnitude as those predicted in the single-dose deterministic simulations: AUC_{inf}, FDp, and F increased by 25% and C_{max} by 17% (**Table 2**)

Figure 1. Model-predicted midazolam plasma concentration profile after 15-mg oral midazolam administration alone and with administration of 12 g oral trofinetide: A) linear and B) semi-logarithmic axes



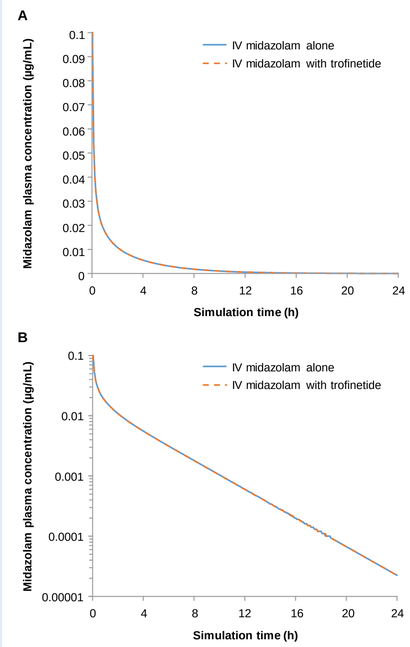
h, hours

Figure 2. Model-predicted trofinetide concentrations in intestinal enterocytes after 12-g oral solution administration



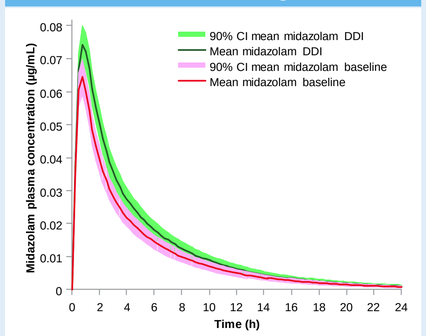
h, hours; IC_{50}, concentration of trofinetide inhibiting 50% of CYP3A4 activity

Figure 3. Model-predicted midazolam plasma concentration profile after 2-mg IV midazolam administration alone and 2 hours after administration of 12 g oral trofinetide: A) linear and B) semi-logarithmic axes



h, hours; IV, intravenous

Figure 4. DDI population simulation output for midazolam exposure after 15-mg oral midazolam administration alone and with 12 g oral trofinetide



CI, confidence interval; DDI, drug-drug interaction; h, hours

Table 2. Population simulation summary statistics for oral midazolam drug interaction with oral trofinetide administration[a]

Midazolam PK endpoint	Mean	CV (%)	Min	Max	Geometric mean	90% CI	Natural log-transformed 90% CI
FDp (%)							
DDI	58.4	19.6	18.2	79.5	57.1	56.5, 60.3	55.0, 59.3
Baseline	47.8	26.8	8.91	72.9	45.7	45.7, 49.9	43.3, 48.2
Ratio	1.26	11.6	1.09	2.05	1.25	1.23, 1.28	1.23, 1.27
F (%)							
DDI	33.2	34.9	8.54	62.2	31.0	31.3, 35.2	29.0, 33.1
Baseline	27.1	39.5	5.86	56.2	24.8	25.3, 28.9	23.0, 26.7
Ratio	1.26	11.6	1.09	2.05	1.25	1.23, 1.28	1.23, 1.27
Plasma C_{max} (µg/mL)							
DDI	0.0777	44.7	0.0097	0.186	0.0692	0.0719, 0.0835	0.0634, 0.0754
Baseline	0.0677	48.1	0.0064	0.161	0.0592	0.0623, 0.0731	0.0539, 0.0650
Ratio	1.18	12.8	1.04	2.10	1.17	1.15, 1.20	1.15, 1.19
Plasma T_{max} (h)							
DDI	0.835	32.0	0.45	1.50	0.795	0.790, 0.879	0.755, 0.837
Baseline	0.754	31.6	0.35	1.35	0.720	0.714, 0.794	0.685, 0.757
Ratio	1.11	7.82	0.89	1.33	1.10	1.09, 1.12	1.09, 1.12
Plasma AUC_{inf} (ng × h/mL)							
DDI	341	76.5	29.0	1283	253	298, 385	221, 290
Baseline	277	79.2	23.2	1091	202	241, 313	176, 233
Ratio	1.26	11.6	1.09	2.05	1.25	1.23, 1.28	1.23, 1.27

[a]Oral midazolam (15 mg) was administered concurrently with oral trofinetide (12 g) in a crossover design with n = 100

AUC_{inf}, area under the concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed concentration; CV, coefficient of variation; DDI, drug-drug interaction; F, bioavailability; FDp, fraction of oral dose reaching the portal vein; h, hours; min, minimum; max, maximum; PK, pharmacokinetic; T_{max}, time to maximum observed concentration

CONCLUSIONS

- The PBPK model suggests that systemic trofinetide levels do not impact CYP3A4 metabolism in the liver
- However, after oral administration of the therapeutic dose, trofinetide has the potential to be a weak inhibitor of CYP3A4 metabolism locally in the gut because of the relatively high concentrations of trofinetide present in the intestinal wall immediately after dosing

REFERENCES

1. Neul JL, et al. *Nat Med*. 2023;29(6):1468–1475.
2. DAYBUE (trofinetide) [package insert]. San Diego, CA: Acadia Pharmaceuticals Inc.; 2023.
3. Jian L, et al. *Eur J Paediatr Neurol*. 2007;11(5):310–317.
4. Steffenburg U, et al. *Acta Paediatr*. 2001;90(1):34–39.
5. Teo YL, et al. *Br J Clin Pharmacol*. 2015;79(2):241–253.
6. Wilkinson GR. *N Engl J Med*. 2005;352(21):2211–2221.
7. Johannessen SI, Landmark CJ. *Curr Neuropharmacol*. 2010;8(3):254–267.
8. Kolars JC, et al. *Pharmacogenetics*. 1994;4(5):247–259.
9. Paine MF, et al. *Drug Metab Dispos*. 2006;34(5):880–886.
10. Klein K, Zanger UM. *Front Genet*. 2013;4:12.
11. Li AP, et al. *Toxicology*. 1995;104(1–3):1–8

ACKNOWLEDGMENTS

The study was supported by Acadia Pharmaceuticals Inc. (San Diego, CA, USA). Medical writing support was provided by Stuart Murray, MSc, of Evidence Scientific Solutions, Inc. and funded by Acadia Pharmaceuticals Inc.

DISCLOSURES

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

To receive a copy of this poster, scan QR code via barcode reader application.

By requesting this content, you agree to receive a one-time communication using automated technology. Message and data rates may apply. Links are valid for 30 days after the congress presentation.

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

ACADIA®