Population Pharmacokinetic Modeling of Teduglutide to Support Dosing in Pediatric Patients with Short Bowel Syndrome

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Abstract

Objectives: Teduglutide is a mucosally active analog of human endogenous meal stimulated hormone, glucagon-like peptide-2 (GLP-2). Population PK modeling was performed to support dosing of teduglutide for the treatment of short bowel syndrome (SBS) in pediatrics patients.

Methods: Teduglutide concentrations in 266 adult patients and 37 pediatric patients were included in the analysis and sources of variability were explored (age, body weight, gender race, markers of renal/liver function). Simulations were performed to compare teduglutide exposure in adult and pediatric patients following daily subcutaneously (SC) administrations of 0.025, 0.05, and 0.10 mg/kg (NONMEM Version VII; Trial Simulator® V2.2.).

Results: Median (range) age and body weight in the population were 34.9 years (1.67-79.0) and 67.6 kg (10.1-127), respectively. A one-compartment model with first-order absorption and allometric components accounting for size resulted in adequate goodness-of-fit. Markers of renal/hepatic functions were not significant covariates. Mean maximum concentration (C_{max}) of teduglutide consistently ranged between 35.7 and 38.7 ng/mL across age groups after a 0.05 mg/kg dose, whereas the area under the curve (AUC) gradually decreased with age from an average of 313 ng.h/mL in adults to 101 ng.h/mL in children between 1 and 2 years of age.

Conclusions: Clinical data in conjunction with C_{max} were considered to support teduglutide dose selection since AUC was previously shown not to correlate with efficacy. Therefore, the 0.05 mg/kg dose, which was well tolerated and effective across age groups, was selected as the safe and effective dose in pediatric patients with SBS.

Background

- Teduglutide is a mucosally active analog of human endogenous meal stimulated hormone, glucagone-like peptide 2 (GPL-2). Teduglutide contains a single amino acid substitution at the second position of the N-terminus which confers resistance to enzymatic degradation by dipeptidyl peptidase IV (DPP-IV).
- Teduglutide is indicated for the treatment of short bowel syndrome (SBS).[1] SBS typically occurs when there is less than 200 centimeters of functioning small bowel and manifests as a collection signs and symptoms such as malabsorption, diarrhea, steatorrhea, and fluid electrolyte disturbances. SBS usually results from surgical resection of the bowel secondary to Crohn's disease, mesenteric vascular complications, trauma, extensive aganglionosis, etc.[2,3]

Objective

- The objective of this project was to perform a population pharmacokinetic (PK) analysis of teduglutide by combining PK data from the adult population and from a recently completed Phase III study in pediatric patients. The final PK model was used to perform simulations to ultimately support dosing in pediatric patients with SBS.

Methodology

- A 12-week pharmacokinetic (PK), safety, and pharmacodynamic study of teduglutide in pediatric patients aged 1 through 17 years, with short bowel syndrome who are dependent on parenteral support was performed (Study NCT01952080). Patients received repeated SC administrations (0.0125, 0.025, and 0.05 mg/kg/day) for 12 weeks. To determine the plasma concentrations of teduglutide, blood samples were collected at pre-dose, at 1 and 6 hours post-dose at start of treatment and at pre-dose, 2 and 4 hours post-dose at Week 4.
- Concentration-time data of teduglutide included 5 Phase I adult studies, 3 Phases II/III adult studies and this pediatric study.
- Allometric functions were included on CL/F, Vc/F and Ka of teduglutide to take into account the effect of body weight on PK parameters as presented below.

$$CL_j = CL_x X \left(\frac{WT_j}{70}\right)^{WTCL} \qquad V_j = V_x X \left(\frac{WT_j}{70}\right)^{WTV} \qquad Ka_j = Ka_x X \left(\frac{WT_j}{70}\right)^{WTka}$$

- Model discrimination was performed based on statistical estimator of goodness of fit (objective function) and graphical display of data (observed vs. predicted, weight residuals).
- Clinical trial simulations were performed with the objective to compare the predicted systemic exposure to teduglutide at steady-state between adults and pediatric SBS patients of various age categories. The subcutaneous dose levels selected for the simulations were 0.025, 0.05 and 0.10 mg/kg q24h for 14 days. The age categories considered were as follows: ≥ 1 year and < 2 years, ≥ 2 years and < 4 years, ≥ 4 years and < 6 years, ≥ 6 years and < 8 years, ≥ 8 years and < 12 years, ≥ 12 years and < 18 years, and adults (≥ 18 years).

Results

Baseline Characteristics

- A total of 303 patients from 9 studies were evaluable for population PK analysis. Descriptive statistics of baseline characteristics of patients are presented in **Table 1**.

Table 1. Descriptive Statistics of Baseline Characteristics (n=303)

Characteristics	Mean (CV%) Median [Min, Max]
Age (years)	34.9 (50.1) 34.0 [1.67, 79.0]
Weight (kg)	65.0 (35.5) 67.6 [10.1, 127]
ALT (U/L)	34.7 (106.5) 24.0 [3.00, 412]
AST (U/L)	30.7 (81.1) 23.0 [10.0, 297]
Bilirubin (mg/dL)	0.520 (98.8) 0.480 [0.0500, 7.80]
GGT (U/L)	40.9 (115.7) 26.0 [7.00, 382]
CRCL (mL/min)	105 (36.2) 105 [26.0, 236]

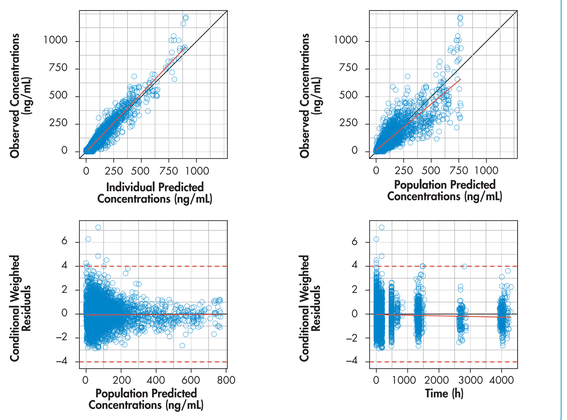
ALT: alanine aminotransferase, AST: aspartate aminotransferase, GGT: gamma-glutamyl transferase, CRCL: creatinine clearance.

- Median (range) age and body weight in the population were 34.9 years (1.67 – 79.0) and 67.6 kg (10.1 – 127), respectively. The population consisted of 189 (62.4%) male and 114 (37.6%) female patients. The population included 145 (47.9%) healthy individuals, 152 (50.2%) patients with SBS/Crohn's disease and 6 (2.0%) patients with hepatic impairment. The vast majority of patients were Caucasians (83.5%) followed by African-American (12.5%).
- The dataset included 4858 measurable teduglutide concentrations.

Population PK Modeling

- After inclusion of body weight as a structural covariate through allometric functions applied to parameters Ka, CL/F and Vc/F, no additional covariates improved the fit. The final population PK model consisted of a one-compartment model with a first-order absorption and a lag time. Goodness of fit of the final population PK model is presented in **Figure 1**.

Figure 1. Goodness of Fit of Final Population PK Model



- The PK model adequately fitted teduglutide concentrations (individual and population level) and CWRES values were homogeneously distributed around 0.
- Typical population PK parameters of teduglutide in adults and pediatric SBS patients are presented in **Table 2**.

Table 2. Final Model Population PK Parameter Estimates of Teduglutide in Adults and Pediatric SBS Patients

Population PK Parameters	Typical values (RSE%)	Between-Patient Variability (%) (RSE%)
Absorption Parameters		
Ka (h^{-1})	0.293 x (Body Weight/70)$^{-0.210}$ (2.93)	39.2 (5.92)
ALAG (h)	0.169 (4.94)	0 Fixed (NA)
Disposition Parameters		
CL/F (L/h)	11.9 x (Body Weight/70)$^{0.388}$ (2.06)	30.5 (7.68)
Vc/F (L)	33.8 x (Body Weight/70)$^{1.97}$ (3.80)	45.1 (9.74)
Error Model		
Additive Error (ng/mL)	5.09 (11.1)	NA
Proportional Error (%)	26.2 (4.81)	NA

ALAG = lag time of absorption; CL/F = apparent clearance; Ka = first-order rate of absorption; NA= not applicable; PK= pharmacokinetic; RSE = relative standard error; Vc/F = apparent central volume of distribution.

- Allometric exponents for Ka, CL/F and Vc/F were -0.210, 0.388, and 1.97, respectively. A single value of parameter Ka (0.293 h^{-1} in a 70-kg individual) was able to describe the whole dataset, irrespective of the administration site. All PK parameters were estimated with good precision (RSE% within 12%). Between-patient variability was estimated for Ka, CL/F and Vc/F (39.2%, 30.5%, and 45.1%, respectively). Finally, the residual error was a mixed model combining a 5.09 ng/mL additive error term and a 26.2% proportional error term.
- The covariate analysis confirmed the lack of effect of site of administration, disease status, ethnicity, or sex on PK parameters. Based on the results of the immunogenicity test in study TED-C13-003, only one patient had a positive result for the presence of teduglutide specific antibodies. The presence of antibodies does not seem to affect teduglutide PK parameters. Due to a lack of supporting data, the antibody status could not be tested as a potential covariate.
- Markers of renal and hepatic functions were not detected as significant components explaining the variability of PK parameters of teduglutide. Based on this, maturation functions of renal or liver function were not included in the model.

Simulations

- Simulations were performed to compare teduglutide exposure in adult subjects and pediatric patients following SC dosing of 0.025, 0.05, and 0.10 mg/kg every 24 hours for 14 days. Simulated exposures of teduglutide under steady state conditions are summarized by dose level and age in **Table 3**.

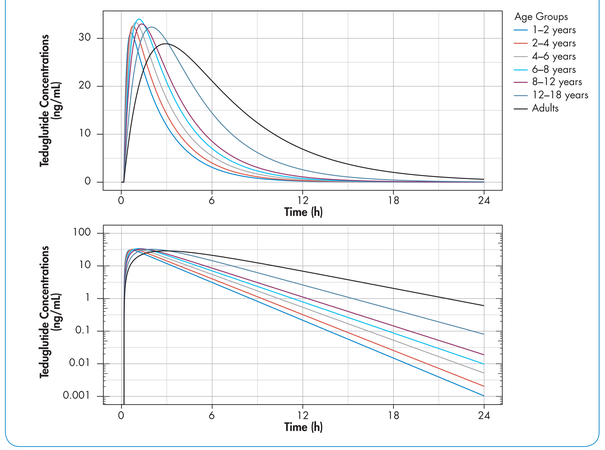
Table 3. Simulated Exposure of Teduglutide Following Repeated Daily SC Dosing of Teduglutide (0.05mg/kg) in Adults and Pediatric SBS Patients

Age Categories	Mean (SD) Median [90% CI]		
	$C_{max,ss}$ (ng/mL)	AUC_{ss} (ng.h/mL)	$C_{12,ss}$ (ng/mL)
Adults	35.7 (12.5) 33.7 [19.8 - 59.8]	308 (106) 293 [169 - 505]	9.69 (6.29) 8.55 [1.89 - 21.6]
12-18 years	38.8 (13.6) 37.2 [21.3 - 65.5]	232 (72.0) 220 [135 - 367]	4.61 (3.32) 3.75 [1.15 - 11.6]
8-12 years	39.2 (15.9) 36.0 [19.2 - 69.3]	174 (56.5) 167 [98.7 - 274]	3.04 (2.15) 2.41 [1.09 - 7.41]
6-8 years	40.2 (16.9) 36.8 [18.6 - 71.1]	159 (54.4) 152 [85.0 - 251]	2.58 (1.68) 2.08 [1.13 - 6.17]
4-6 years	38.2 (15.8) 34.9 [18.2 - 68.7]	134 (44.0) 128 [76.4 - 217]	2.13 (1.01) 1.84 [1.08 - 4.04]
2-4 years	36.6 (16.4) 33.9 [15.6 - 65.3]	111 (38.5) 104 [59.1 - 182]	1.83 (0.95) 1.53 [1.04 - 3.35]
1-2 years	35.2 (16.8) 31.6 [14.6 - 67.4]	95.0 (33.5) 89.3 [50.7 - 159]	1.73 (0.716) 1.47 [1.04 - 2.96]

AUC_{ss} = area under the concentration-time curve under steady-state; $C_{12,ss}$ = steadystate concentration at 12 h post dose; CI = confidence interval; $C_{max,ss}$ = maximum (peak) concentration at steadystate; NA = not applicable; SD = standard deviation.

- Mean simulated $C_{max,ss}$ of teduglutide were consistent across age categories and ranged between 31.6 - 40.2 ng/mL. For pediatric patients (0.05 mg/kg), the range of observed $C_{max,ss}$ was 18.8 - 58.8 ng/mL and was within the range of simulated $C_{max,ss}$ (i.e., 14.6 – 71.1 ng/mL). For adult patients, $C_{max,ss}$ ranges were 16.3 – 72.0 ng/mL and 32.9 - 72.1 ng/mL, respectively, and were comparable to simulated $C_{max,ss}$ range (i.e., 19.8 - 59.8 ng/mL).
- AUC_{ss} values were age-dependent and gradually decreased with age from a mean of 308 ng.h/mL in adults to 95.0 ng.h/mL in children between 1 and 2 years of age. Consistent with the AUC_{ss}, simulated concentrations of teduglutide at 12 h postdose were age-dependent and gradually decreased with age. Mean $C_{12,ss}$ ranged from 1.73 to 4.61 ng/mL, respectively following dosing of 0.05 mg/kg.
- Predicted concentration-time profile of teduglutide following SC administration of 0.05 mg/kg in adult and pediatric patients are presented in **Figure 2**.

Figure 2. Predicted Concentration-Time Profile of Teduglutide Following SC Administration of 0.05 mg/kg in Adult and Pediatric Patients with SBS (Linear and Semi-Log Scales)



Conclusions

- Simulation results indicated that pediatric patients (1-17 years) are expected to display similar steady state C_{max} values of teduglutide as adults. On the other hand, simulated AUC_{ss} were highly age-dependent and gradually decreased from adults to children between 1 and 2 years of age.
- Clinical data in conjunction with C_{max} were considered to support teduglutide dose selection since AUC was previously shown not to correlate with efficacy. Therefore, the safety profile of the 0.05 mg/kg dose, which was well tolerated and effective across age groups, was selected as the safe and effective dose in pediatric patients with SBS.

Acknowledgments

This study was supported by Shire Development LLC., Lexington, MA, USA. Editorial support was funded by Shire International GmbH, Zug, Switzerland and provided by Shirley Teng, PhD, CMPP, of Excel Scientific Solutions.

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Poster presented at the American Society for Clinical Pharmacology and Therapeutics (ASCPT) Annual Meeting; March 15–18, 2017; Washington DC, USA