Teduglutide, a glucagon-like peptide-2 (GLP-2) analog, is currently being evaluated for the treatment of short-bowel syndrome, Crohn’s disease, and other gastrointestinal disorders. The pharmacokinetics, safety, and tolerability of teduglutide in healthy subjects (N = 64) were assessed following daily subcutaneous administrations for 8 days in a double-blinded, randomized, placebo-controlled, ascending-dose study. Teduglutide treatments were administered as a 50-mg/mL (10, 15, 20, 25, 30, 50, and 80 mg) or 20-mg/mL (20 mg) formulation. Blood samples were collected on days 1 and 8, and plasma concentrations of teduglutide were measured using a liquid chromatography/tandem mass spectrometry method. Mean systemic exposures to teduglutide were very similar on days 1 and 8, suggesting minimal, if any, accumulation following once-daily repeated administrations. The apparent clearance of teduglutide following administration of the 50-mg/mL formulation was constant over the dose range, with mean values in male and female subjects of 0.155 and 0.159 L/h/kg, respectively. Peak plasma concentrations and total exposure of teduglutide after subcutaneous injection of a 20-mg/mL formulation (1.0 mL) were approximately 15% and 78% higher than those observed with the 50-mg/mL formulation (0.4 mL), respectively. Teduglutide treatments were safe and well tolerated. All but 1 adverse event was assessed as mild or moderate in severity. No relationship between teduglutide treatments and frequency of adverse events was observed, with the exception of injection site pain, which increased as a function of dose and injected volume. Results from the current study will assist in the dose selection in future efficacy studies.

Keywords: Teduglutide; multiple-ascending dose; subcutaneous; pharmacokinetics; safety and tolerability

Journal of Clinical Pharmacology, 2008;48:1289-1299
© 2008 the American College of Clinical Pharmacology

Glucagon-like peptide-2 (GLP-2) is a naturally occurring peptide involved in the regeneration, maintenance, and repair of the intestinal epithelium. Glucagon-like peptide-2 is composed of 33 amino acids and is located at the carboxyterminal end of proglucagon. Although GLP-2 activity is limited by its rapid rate of degradation via circulating dipeptidylpeptidase IV (DPP-IV) enzymes, ongoing research suggests that GLP-2 may be a promising therapeutic adjuvant for the treatment of patients with various forms of...
Teduglutide (ALX-0600, [gly²]-hGLP-2) is a synthetic analog of human GLP-2 that contains a single amino acid substitution at the second position of the N-terminus, which confers resistance to enzymatic degradation by DPP-IV. Teduglutide has been shown to elicit a number of pharmacological responses in the gastrointestinal tract, including an increase of small and large intestinal weight in mice, rats, and monkeys. Teduglutide (ALX-0600, [gly²]-hGLP-2) is a synthetic analog of human GLP-2 that contains a single amino acid substitution at the second position of the N-terminus, which confers resistance to enzymatic degradation by DPP-IV. Teduglutide has been shown to elicit a number of pharmacological responses in the gastrointestinal tract, including an increase of small and large intestinal weight in mice, rats, and monkeys.

The bioavailability of teduglutide was evaluated following administration of a 0.12-mg/kg dose level administered intravenously (IV) and subcutaneously (SC) in the abdomen in 12 healthy subjects (Protocol No. CLO600-006). The bioavailability of teduglutide after SC administration was 87.1%, and the mean terminal elimination half-life was 3.20 hours. In another phase I study, the relative bioavailability of an SC injection of 10 mg teduglutide in the thigh and arm, relative to the abdomen, was evaluated in 16 healthy subjects. Relative bioavailability of teduglutide was 86.5% and 89.2%, respectively, for thigh and arm sites relative to abdomen injection.

Teduglutide is currently evaluated for the treatment of short-bowel syndrome (SBS) and other gastrointestinal disorders. Short-bowel syndrome typically occurs when there is less than 200 cm of functioning small bowel and manifests as a collection of signs and symptoms such as malabsorption, diarrhea, steatorrhea, fluid and electrolyte disturbances, and malnutrition. Short-bowel syndrome usually results from surgical resection of bowel secondary to Crohn’s disease, mesenteric vascular complications, trauma, extensive aganglioneosis, or as a congenital condition in infants born with intestinal atresia. Overall, data from ongoing clinical trials suggest that teduglutide may have the ability to enhance the intestinal absorptive capacity in patients with SBS.

Based on clinical studies performed in SBS patients, the efficacy and safety of teduglutide were demonstrated following daily administrations of doses up to 0.15 mg/kg/day. Teduglutide is also being evaluated for the management of Crohn’s disease, a chronic inflammatory bowel disorder characterized by patchy granulomatous inflammation of any part of the gastrointestinal tract and associated with chronic morbidity. Crohn’s disease has a prevalence of about 0.1% in many developed countries and is thought to result from a combination of influences, including genetics, immune system function, and environmental factors. Crohn’s disease is characterized by repeated episodes (remission and relapse) of intestinal mucosal inflammation and is associated with a spectrum of clinical complications such as fissure, fistulae, strictures, and abscesses, even with optimal treatment. Despite intense investigation, the exact etiology of Crohn’s disease remains unknown. Crohn’s disease is generally managed by a variety of pharmacological agents, including infliximab, azathioprine, 6-mercaptopurine, methotrexate, and corticosteroids. Present therapeutic options for Crohn’s disease with both anti-inflammatory and immunosuppressive drugs are limited and may be associated with severe side effects.

The current study was designed to determine the pharmacokinetics, safety, and tolerability of teduglutide following multiple subcutaneous administrations in a double-blinded, randomized, placebo-controlled, ascending-dose study. In addition, teduglutide was administered as 20- and 50-mg/mL formulations to evaluate whether this affected its pharmacokinetics, safety, and tolerability profile. The teduglutide dose range started at the highest previously investigated clinical dose up to a maximum of 80 mg, which was considered the highest feasible dose given volume constraints. In nonhuman primate toxicity studies, no organ toxicity was observed up to doses of 25 mg/kg/day.

**MATERIALS AND METHODS**

**Study Design and Treatments**

This was a single-center, double-blinded, randomized, placebo-controlled study. Separate cohorts of healthy subjects were administered ascending doses of teduglutide or placebo as once-daily subcutaneous injections in the abdomen over 8 days. In each cohort, 12 subjects were randomized to either active (9) or placebo (3) treatment. Teduglutide (ALX-0600, [gly²]-hGLP-2) doses and formulations used in each cohort are presented in Table I. The injection site was rotated over the 4 quadrants of the abdomen, and each injection site was used twice. For subjects receiving the 80-mg dose, 2 separate 40-mg injections (considered to be 1 dose) were administered almost simultaneously, within the same quadrant of the abdomen 3 to 4 cm apart from one another. The second injection was administered medial and central to the initial injection. Placebo consisted of the same excipient solution as the teduglutide treatment. Placebo for subcutaneous injection was provided as a lyophilized powder containing L-histidine, mannitol, and monobasic and dibasic sodium phosphate. The injection volume of placebo was the same as that for teduglutide for a specific cohort and was administered subcutaneously.
Subjects arrived at check-in (day –1) to the clinic the evening prior to the drug administration (at least 12 hours prior to dosing on day 1) and were confined at the clinic for approximately 8.5 days. Following admission on day –1, clinical and laboratory assessments were performed, and subjects meeting all eligibility criteria were dosed on day 1. The original study protocol and subject informed consent forms (ICFs) were approved in writing by an institutional review board/independent ethics committee (IRB/IEC) before the enrollment of any subjects (Aspire IRB, La Mesa, California). Prior to the initiation of the next scheduled cohort(s), safety and tolerability data were reviewed and assessed by an independent safety review panel (ISRP). The study was performed in accordance with International Conference on Harmonization (ICH) good clinical practice (GCP) guideline ICH E6 (May 1, 1996) and applicable local regulatory requirements. The regulatory authorities and/or IRB/IECs were informed of amendments to the protocol, any serious adverse events (SAEs), and any other information arising during the course of the study that was deemed to change the risk or safety of the subjects involved in the study.

### Inclusion and Exclusion Criteria

This study enrolled 95 subjects (69 men and 26 women) who were randomized into 8 cohorts. Subjects who met all of the following criteria were enrolled in this study: adult men and women (not pregnant or nursing) who were between 20 and 55 years of age and had a body mass index of 18 to 35, were able to understand and voluntarily willing to sign an ICF, and were willing and able to be confined at the clinical research center for 8.5 days; women who were postmenopausal, surgically sterilized, or of childbearing potential (WOCBP) who were non-lactating and agreed to use an effective form of birth control for at least 30 days prior to study screening, during the study, and at least 30 days after the treatment period; and medically healthy volunteers with normal or clinically insignificant clinical results (laboratory profiles, medical histories, electrocardiograms [ECGs], and physical examination) at screening (days –28 to –2) and check-in (day –1).

Subjects who had any of the following during the screening visit were not eligible for enrollment in this study: (1) donated 1 pint or more of blood or blood products within 56 days prior to the study and/or had a plasma donation within 7 days prior to the study; (2) was pregnant or became pregnant; (3) participated in any other investigational drug trial within 30 days prior to study entry and until study completion; (4) had a physical examination/medical history that indicated a clinical condition or concurrent illness; (5) had a history or presence of clinically significant cardiovascular, pulmonary, hepatic, renal, hematological, gastrointestinal, endocrine, immunologic, dermatologic, neurological, or psychiatric disease; (6) had history or evidence of congenital nonhemolytic hyperbilirubinemia; (7) had history or evidence of gallstone disease or stomach or intestinal surgery, except that appendectomy was allowed; (8) had evidence of colorectal cancer; (9) had a history or evidence of malabsorption, pancreatic disease, gastrointestinal polyps, or gastrointestinal disorders such as irritable bowel syndrome, Crohn’s disease, or ulcerative colitis; and (10) had a history or evidence of skin rashes or dermatitis. With the exception of oral contraception, a subject was excluded if taking prescription or over-the-counter medication during the 7 days preceding or during the study.

### Safety and Tolerability

Safety data included treatment-emergent adverse events (AEs), injection site reactions, clinical laboratory assessments, vital signs, ECGs, and physical exams. All AEs were coded using MedDRA and summarized by system-organ-class and by high-level term and preferred term for each treatment group. Treatment-emergent AEs were defined as AEs whose onset occurs, severity worsens, or intensity increases after receiving double-blind study drug. An interim safety review was conducted by the ISRP.

---

**Table I** Teduglutide Dose and Formulation Used in Each Treatment Group

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Teduglutide, mg/Dose</th>
<th>Formulation, mg/mL</th>
<th>Volume Per Injection, ml</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10</td>
<td>50</td>
<td>0.2</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>50</td>
<td>0.3</td>
</tr>
<tr>
<td>3A</td>
<td>20</td>
<td>20</td>
<td>1.0</td>
</tr>
<tr>
<td>3B</td>
<td>20</td>
<td>50</td>
<td>0.4</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>50</td>
<td>0.5</td>
</tr>
<tr>
<td>5</td>
<td>30</td>
<td>50</td>
<td>0.6</td>
</tr>
<tr>
<td>6</td>
<td>50</td>
<td>50</td>
<td>1.0</td>
</tr>
<tr>
<td>7</td>
<td>80</td>
<td>50</td>
<td>0.8 (2×)α</td>
</tr>
</tbody>
</table>

α Each 80-mg dose was administered as 2 injections of 0.8 mL each administered 3 to 4 cm apart within a single quadrant of the abdomen.
for each completed cohort. Alternate and repeat doses were selected versus those described in the original dosing scheme (up to a maximum of 80 mg of teduglutide) based on a recommendation by the ISRP and approval by the sponsor in conjunction with the principal investigator. Treatment-emergent signs and symptoms (TESSs) were defined as AEs whose onset occurs, severity worsens, or intensity increases after receiving the study medication. Any AE with a start date equal to the date of dosing, where the time of the AE cannot definitively place the start of the AE prior to the time of first dosing, was considered treatment emergent.

In accordance with the Declaration of Helsinki, subjects were free to discontinue the study at any time for any or for no reason and without prejudice to further treatment. Adverse events that were not resolved at the end of treatment were to be followed until resolution or until the AE was judged by the investigator to be stabilized. The sponsor and/or designee was notified prior to premature discontinuation of a subject. The occurrence of any of the following events was to necessitate premature discontinuation of a subject from the study: (1) occurrence of an SAE thought to be related to study drug and not alleviated by symptomatic treatment, (2) development of intolerable AEs as evaluated by the investigator, (3) death of the subject, (4) unwillingness to continue in the clinical study, (5) lack of subject compliance with the protocol, (6) investigator decision (investigator must have conferred with the sponsor and/or designee prior to the subject’s discontinuation), (7) decision to stop the study or dosing cohort for administrative reasons or in conjunction with the ISRP, and (8) subjects who received study drug and were then prematurely withdrawn from the clinical study were not to be replaced.

During the course of dosing, if a subject’s aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) value(s) was ≥2.5 times the upper limit of normal (ULN), irrespective of the subject’s treatment group, the subject was to receive matching placebo for the rest of the dosing period, and values were monitored until return to normal. Subjects remained confined at the site for the scheduled dosing period and remain blinded to the treatment.

**Blood Sampling and Analytical Assay**

Blood samples for pharmacokinetic (PK) analysis of teduglutide were collected at 0 hours (within 30 minutes prior to dosing) and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 6, 8, 10, 12, and 24 hours after dosing on days 1 and 8. Blood samples were collected in 6-mL-draw, green-top, plastic Vacutainer Hemogard evacuated collection tubes (containing sodium heparin). Following centrifugation, plasma aliquots were transferred into 2 appropriately labeled storage tubes and frozen at –80°C pending analytical assay. Plasma concentrations of teduglutide were assayed using a liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay with an analytical range of 1.00 to 120 ng/mL (SCIEX API 4000, Concord, Canada). Briefly, an aliquot of human plasma containing the internal standard (ALX-0600-IS) was extracted using an automated protein precipitation procedure. Multiple-charged positive ions (4+) were monitored in the multiple-reaction monitoring (MRM) model. The following ion transition m/z was monitored for teduglutide and the internal standard: 938.7→234.8 and 944.1→235.2, respectively. Quantitation was by peak ratio. Inter- and intrabatch precision and accuracy were assessed at low, medium, and high quality control (QC) concentration level (3.0, 30.0, and 90.0 ng/mL, respectively). Interbatch precision (coefficient of variation [CV%]) results were less than 5.0%, and accuracy (percent theoretical) results ranged between 97.8% and 107.7%. Intrabatch precision (CV%) results were less than 4.4%, and accuracy (percent theoretical) results ranged between 102.0% and 109.0%. The lower limit of quantitation (LOQ) of the assay was 1.00 ng/mL. Actual concentration values exceeding the upper range of the analytical curve were diluted with blank plasma to demonstrate the precision and accuracy of the assay following dilution. A QC sample of 500 ng/mL was quantified following the application of an appropriate dilution factor. The intrabatch precision (CV%) result of the 500-ng/mL QC sample was 6.5%, and accuracy (percent theoretical) was 104.4%.

**Pharmacokinetics and Statistics**

The following PK parameters were calculated using noncompartmental methods (WinNonlin Version 5.2, Pharsight Corporation, Mountain View, California): the area under the curve from time 0 to the last measurable concentration (AUCₜₚ) using the linear trapezoidal rule, the area under the curve extrapolated to infinity (AUC₀→∞ + Cₚ/kₑₚ, where Cₚ is the last measurable plasma concentration), the maximum plasma concentration (Cₘₚ), and the time to maximum plasma concentration (tₘₚ), the terminal rate constant of elimination (kₑₚ), and terminal elimination half-life (tₑₚ). Teduglutide concentration values below the LOQ of the assay were set to 0.
In addition, the apparent clearance (CL/F) was calculated as dose/AUC_{∞} and adjusted for body weight of subjects. Dose proportionality of PK parameters of teduglutide was assessed using a power model. A statistical linear relationship between ln-transformed pharmacokinetic parameters AUC_{0-t}, AUC_{0-∞}, and C_{max} on days 1 and 8 and the ln-transformed dose was fitted. As a first step, the statistical significance of a dose-by-day interaction was verified. Second, the statistical linear relationship between the ln-transformed parameters and ln-transformed dose was verified by including cubic and quadratic effects, respectively. The statistical linear relationship was concluded if the quadratic and cubic terms were not statistically significant or if the effects were statistically significant. If the statistical linear relationship was established, 95% confidence intervals for the slope of ln-transformed parameters were to be calculated. Dose proportionality was established if a statistically significant linear relationship between ln-transformed parameters and ln-transformed dose was verified. As a first step, the statistical significance of a dose-by-day interaction was verified. Second, the statistical linear relationship between the ln-transformed parameters and ln-transformed dose was verified by including cubic and quadratic effects, respectively. The statistical linear relationship was concluded if the quadratic and cubic terms were not statistically significant or if the effects were statistically significant. If the statistical linear relationship was established, 95% confidence intervals for the slope of ln-transformed parameters were to be calculated. Dose proportionality was established if a statistical linear relationship was demonstrated and if the 95% confidence intervals for these parameters include the value of 1. The above assessments were performed using the SAS Mixed procedure.

Analyses of variance (ANOVs) were used to compare ln-transformed AUC_{0-t}, AUC_{0-∞}, and C_{max} of teduglutide between cohorts B1 and B2 (20-mg doses in 20- or 50-mg/mL formulations) on days 1 and 8. The ANOVA model included formulation and day (1 and 8) as a fixed effect and subject as a random effect. The ANOVA included calculation of least squares means (LSMs), the difference between regimen LSMs, and the standard error associated with this difference. Statistical analyses were performed using the SAS Mixed procedure. Ratios of LSMs (cohort B1/B2) were calculated using the exponentiation of the LSM from the analyses on the ln-transformed AUC_{0-t}, AUC_{0-∞}, and C_{max} of teduglutide. Ninety percent confidence intervals for the ratios were derived from the ANOVA.

RESULTS

Demographics

For subjects randomized to placebo and teduglutide treatments, mean (± SD) values for age (34.4 ± 10.6 and 32.1 ± 9.75 years, respectively), weight (80.3 ± 17.0 and 82.0 ± 15.2 kg, respectively), height (173.8 ± 7.10 and 172.9 ± 10.8 cm, respectively), and body mass index (BMI; 26.5 ± 4.95 and 27.5 ± 5.28 kg/m², respectively) were similar. A similar percentage of male and female subjects received placebo (29.2% vs 26.8%, respectively) and teduglutide treatments (70.8% vs 73.2%, respectively). Overall, demographic characteristics of subjects in the placebo and teduglutide groups were comparable.

Pharmacokinetics

Mean plasma concentration-time profiles of teduglutide following multiple ascending subcutaneous administrations of the 50-mg/mL formulation (male and female subjects combined) on days 1 and 8 are presented in Figure 1. Overall, the pharmacokinetics of teduglutide were well characterized on both days because peak plasma concentrations were more than 20-fold higher than the LOQ of the assay. Peak plasma concentrations of teduglutide were observed at approximately 4 hours after drug administration on days 1 and 8. Mean predose plasma concentrations of teduglutide on day 8 were very low, suggesting minimal accumulation of the drug following repeated subcutaneous administrations. Descriptive statistics of PK parameters of teduglutide following administration of the 50-mg/mL formulations (combined gender) on days 1 and 8 are presented in Tables II and III, respectively. Mean AUC_{0-t}, AUC_{0-∞}, and C_{max} values of teduglutide were similar on days 1 and 8, confirming that minimal accumulation of the drug occurs following repeated once-daily SC administrations. Teduglutide was readily absorbed and then eliminated rapidly, with mean elimination half-life values ranging from 3.17 to 5.53 hours on day 1 and from 2.99 to 4.63 on day 8. These results suggest that the PK of teduglutide is linear because its elimination half-life remained very similar after single and multiple subcutaneous administrations across all dose ranges. Overall, mean CL/F values remained relatively constant over the dose range studied on days 1 and 8. As a result, CL/F values in men and women were pooled across cohorts to assess any gender-related trend. Mean CL/F values in male and female subjects were 0.155 and 0.159 L/h/kg, respectively, suggesting no gender-related difference in the apparent clearance of teduglutide.

Dose proportionality was evaluated using a power model. Pharmacokinetic parameters (AUC_{0-t}, AUC_{0-∞}, and C_{max}) on days 1 and 8 were pooled in the analysis because the dose-by-day interaction term was not statistically significant. A linear relationship best described the relationship between dose and PK parameters (AUC_{0-t}, AUC_{0-∞}, and C_{max}) because cubic and quadratic terms were not statistically significant. Slope estimates (95%) for AUC_{0-1st} and AUC_{0-∞}
**Table II**  
Arithmetic Mean (± SD) Pharmacokinetic Parameters Following Subcutaneous Administration of Teduglutide in Healthy Subjects on Day 1

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cohort 1 10 mg qd (n = 9)</th>
<th>Cohort 2 15 mg qd (n = 9)</th>
<th>Cohort 3A 20 mg qd (n = 9)</th>
<th>Cohort 4 25 mg qd (n = 9)</th>
<th>Cohort 5 30 mg qd (n = 9)</th>
<th>Cohort 6 50 mg qd (n = 9)</th>
<th>Cohort 7 80 mg qd (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀⁻𝜏, ng·h/mL</td>
<td>774 (128)</td>
<td>1172 (444.4)</td>
<td>1429 (162.2)</td>
<td>1658 (310.0)</td>
<td>2189 (628.2)</td>
<td>4166 (864.6)</td>
<td>5113 (1002.1)</td>
</tr>
<tr>
<td>AUC₀⁻∞, ng·h/mL</td>
<td>857 (146.1)</td>
<td>1423 (483.2)</td>
<td>1528 (213.2)</td>
<td>1784 (653.1)</td>
<td>2634 (1295.3)</td>
<td>4526 (1020.3)</td>
<td>5707 (972.2)</td>
</tr>
<tr>
<td>Cₘₚₓₓ, ng/mL</td>
<td>101 (38.1)</td>
<td>175 (89.3)</td>
<td>152 (54.5)</td>
<td>162 (51.3)</td>
<td>250 (169.3)</td>
<td>456 (96.5)</td>
<td>562 (355.1)</td>
</tr>
<tr>
<td>tₘₚₓₓ, h⁻</td>
<td>4.00</td>
<td>3.50</td>
<td>4.00</td>
<td>6.00</td>
<td>6.00</td>
<td>4.00</td>
<td>6.00</td>
</tr>
<tr>
<td>Cₘₚₓₓ, h</td>
<td>(3.00-6.00)</td>
<td>(1.50-12.0)</td>
<td>(3.00-12.0)</td>
<td>(3.50-12.0)</td>
<td>(3.00-8.00)</td>
<td>(2.50-8.00)</td>
<td>(3.00-12.0)</td>
</tr>
<tr>
<td>CL/F, L/h/kg</td>
<td>0.151 (0.0167)</td>
<td>0.158 (0.0355)</td>
<td>0.157 (0.0255)</td>
<td>0.162 (0.0264)</td>
<td>0.164 (0.0486)</td>
<td>0.158 (0.0153)</td>
<td>0.165 (0.0363)</td>
</tr>
</tbody>
</table>

*Median (range).*

**Table III**  
Arithmetic Mean (± SD) Pharmacokinetic Parameters Following Subcutaneous Administration of Teduglutide in Healthy Subjects on Day 8

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Cohort 1 10 mg qd (n = 8)</th>
<th>Cohort 2 15 mg qd (n = 8)</th>
<th>Cohort 3A 20 mg qd (n = 9)</th>
<th>Cohort 4 25 mg qd (n = 9)</th>
<th>Cohort 5 30 mg qd (n = 9)</th>
<th>Cohort 6 50 mg qd (n = 8)</th>
<th>Cohort 7 80 mg qd (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC₀⁻𝜏, ng·h/mL</td>
<td>740 (144.7)</td>
<td>1135 (565.8)</td>
<td>1418 (288)</td>
<td>1529 (290.3)</td>
<td>2266 (679.3)</td>
<td>4057 (987.8)</td>
<td>5088 (1209)</td>
</tr>
<tr>
<td>AUC₀⁻∞, ng·h/mL</td>
<td>863 (140.1)</td>
<td>1289 (663.1)</td>
<td>1790 (364)</td>
<td>1924 (928.7)</td>
<td>2433 (651.4)</td>
<td>4316 (894.8)</td>
<td>5377 (910)</td>
</tr>
<tr>
<td>Cₘₚₓₓ, ng/mL</td>
<td>104 (36.2)</td>
<td>186 (105.4)</td>
<td>165 (57.4)</td>
<td>150 (47.8)</td>
<td>211 (101.6)</td>
<td>454 (156.6)</td>
<td>555 (329.8)</td>
</tr>
<tr>
<td>tₘₚₓₓ, h⁻</td>
<td>4.00</td>
<td>2.75</td>
<td>4.00</td>
<td>4.00</td>
<td>5.00</td>
<td>3.75</td>
<td>4.00</td>
</tr>
<tr>
<td>Cₘₚₓₓ, h</td>
<td>(3.00-6.00)</td>
<td>(0.52-4.00)</td>
<td>(2.50-6.00)</td>
<td>(3.00-10.0)</td>
<td>(3.00-6.02)</td>
<td>(2.50-6.00)</td>
<td>(3.00-8.00)</td>
</tr>
<tr>
<td>CL/F, L/h/kg</td>
<td>0.151 (0.0234)</td>
<td>0.148 (0.0345)</td>
<td>0.137 (0.0256)</td>
<td>0.161 (0.0234)</td>
<td>0.160 (0.0264)</td>
<td>0.165 (0.0286)</td>
<td>0.174 (0.0235)</td>
</tr>
</tbody>
</table>

*Median (range).*
PHARMACOKINETICS, SAFETY, AND TOLERABILITY OF TEDUGLUTIDE

were 0.95 (0.86-1.04) and 0.91 (0.81-1.01), respectively. Dose proportionality in the AUC_{0-t} and AUC_{0-∞} of teduglutide was therefore confirmed over the 10- to 80-mg dose range because the 95% confidence intervals around the slope values included the value 1. Slope estimates (95%) for C_{max} were 0.80 (0.64-0.96), suggesting a less than proportional increase from 10 to 80 mg because the upper confidence interval was below 1.00. Following removal of the highest dose level (ie, 80 mg, the only dose level administered as 2 injections of 0.8 mL), dose proportionality in C_{max} of teduglutide was confirmed, with 95% confidence intervals (0.61 to 1.04) including the value 1.

An ANOVA model was used to compare ln-transformed PK parameters of teduglutide (AUC_{0-t}, AUC_{0-∞}, and C_{max}) after administration of 20 mg in cohort B1 (1.0-mL injection of a 20-mg/mL formulation) and cohort B2 (0.4-mL injection of a 50-mg/mL formulation) on days 1 and 8. Because the day-by-formulation interaction term was not statistically significant for all PK parameters, relative bioavailability was assessed using pooled data from days 1 and 8. Results of the statistical analysis are presented in Table IV. Ratios of LSM for AUC_{0-t}, AUC_{0-∞}, and C_{max} of teduglutide (ratio: 3A/3B) were 122.6%, 115.1%, and 177.7%, with the 90% CI falling outside the 80.0% to 125.0% range. These results suggest that subcutaneous administration of 1.0 mL of a 20-mg/mL formulation of teduglutide (cohort A) resulted in a higher total exposure and peak plasma concentrations of the drug as compared with the 50-mg/mL formulation by approximately 15% and 78%, respectively (Figure 2).

Safety and Tolerability Results

Based on the ISRP review of safety information from cohorts 3A and 3B, the protocol was amended to investigate slightly lower and higher doses levels than 20 mg (ie, 10, 15, and 25 mg, respectively). Following a safety evaluation of these dose levels, the ISRP further allowed dosing with 80 mg. A total of 86 subjects (17 placebo; 69 teduglutide) reported a total of 409 AEs (placebo: n = 70; teduglutide: n = 339). The overall number of subjects reporting AEs and the number of AEs were distributed similarly across all treatment groups. In general, most AEs in each of the treatment groups were rated as mild or moderate in severity. A similar number of events were considered as related and not related to the study drug for all treatment groups. One subject reported a single SAE (left orbital fracture, teduglutide, cohort A) during the study follow-up period (postconfinement) that was not related to study drug. One subject (teduglutide, cohort 3A) reported 1 AE that led to treatment and study discontinuation because the subject displayed a vasovagal-related “seizure” prior to dosing on day 2 that was rated as moderate. This AE was considered related to the administered treatment. No other significant AEs were noted.

The vast majority of AEs were considered related to the study drug across treatment groups. The most frequently reported AEs for teduglutide by preferred term were as follows: abdominal distension (29.6%), abdominal pain (16.9%), constipation (22.5%), nausea (14.1%), injection site erythema (15.5%), injection site pain (35.2%), headache (23.9%), increased ALT (18.3%), and increased AST (14.1%). Although
individual changes in liver function test (LFT) occurred during the study, the changes were transient in nature, and the frequency of subjects displaying changes was similar to that observed in the placebo group, and values returned to normal by the end of the study (ie, day 14). Overall, increases in LFTs were mild, with the exception of 3 subjects whose values increased by more than 2-fold. The transient nature of liver enzymes changes may be related to confinement of subjects in a clinical pharmacology unit rather than treatment with study drug.15 All other events were reported for less than 10% of subjects in the teduglutide and placebo groups.

For AEs pertaining to the gastrointestinal system and general disorders, the frequency of events recorded for the teduglutide groups was generally greater when compared with placebo. A summary figure depicting the frequency of occurrence of AEs for the ascending treatments of teduglutide is presented in Figure 3. Although no obvious relationship with increasing dose levels was observed for any body system organ class, a noticeable decrease in the frequency of AE associated with the general disorders and administration site conditions system class were observed in cohorts 3B, 4, and 5 as compared with those observed in cohorts 3A, 6, and 7. Adverse events observed in the general disorders and administration site conditions system class were mainly injection site pain and appeared to be correlated with the volume injected. A summary figure depicting the frequency of occurrence of injection site pain in each cohort as a function of injected volume is presented in Figure 4. In general, the frequency of injection site pain increased as a function of dose for the 50-mg/mL formulations and correlated with the increase in injection volume (0.25-1.6 mL), with the exception of cohort 2, which displayed an unexpectedly high frequency of injection site pain considering the low volume injected.
Although the source of injection site pain events in cohort 2 remains unknown, all events were rated as mild and did not show time-specific patterns (i.e., the percentage of subjects experiencing injection site pain on days 1, 2, 3, 4, 5, 6, 7, and 8 was 0%, 22.2%, 33.3%, 22.2%, 0.0%, 11.1%, 11.1%, and 0.0%, respectively).

Clinical labs, vitals, and ECGs remained relatively unchanged throughout the duration of the study, with very few values above or below normal limits and with very few clinically significant abnormal findings.

**DISCUSSION**

Crohn’s disease is generally managed by a variety of pharmacological agents, including infliximab, azathioprine, 6-mercaptopurine, methotrexate, and corticosteroids. Present therapeutic options for Crohn’s disease with both anti-inflammatory and immunosuppressive drugs are limited and may be associated with severe side effects. Infliximab, a monoclonal
antibody to tumor necrosis factor-α (TNF-α), has been found to be effective in the treatment of Crohn’s disease. This therapy works by targeting inflammatory pathways but has also been shown to reverse the defect in intestinal permeability found in Crohn’s disease patients. However, about 20% of Crohn’s disease patients fail to respond to this agent, and a recent report suggested there may be an increased risk of lymphoproliferative disorders in patients treated with TNF-α antagonists. Alternatively, recent studies examining growth hormone, which stimulates intestinal growth and repair and decreases intestinal permeability, have shown efficacy in the treatment of Crohn’s disease.

Although clinical studies in SBS patients supported effective teduglutide doses up to 0.15 mg/kg/day for the treatment of SBS, preliminary analysis of dose-response data in a proof-of-concept study in Crohn’s patients suggests a possible need for higher doses in this population. The teduglutide dose range in this study started at the highest investigated clinical dose up to a maximum of 80 mg, which at this time is thought to be the highest dose for additional studies. At a dose of 80 mg, the margins of safety were estimated to be approximately 3.4- and 2.3-fold, based on teduglutide’s exposure observed at the no observed adverse effect level (NOAEL) for nonhuman primates. The NOAELs in the nonhuman primate study were based on injection site reactions; no organ toxicity was observed. The abdomen was chosen as the primary site of injection of teduglutide because subcutaneous administration of 10 mg in the abdomen, thigh, and arm resulted in bioequivalent exposure of teduglutide. As a result, repeated subcutaneous administrations of teduglutide with doses up to 80 mg were investigated in the current study to evaluate its pharmacokinetics, safety, and tolerability in healthy volunteers.

In the current study, teduglutide was readily absorbed and declined with mean t1/2 values ranging from 2.99 to 4.63 hours over the dose range studied. Teduglutide’s elimination half-life in healthy humans is in sharp contrast to the very rapid elimination of native GLP-2 by circulating DPP-IV enzymes, which was reported to be approximately 7 minutes. Although providing resistance to enzymatic degradation, the single amino acid substitution of teduglutide was also shown to provide enhanced binding to the GLP-2 receptor as compared with the native GLP-2 (EC50 of 9.2 ± 0.6 vs 14 ± 2.9 nmol, respectively). The pharmacokinetics of teduglutide were linear across the dose range studied because apparent clearance values remained relatively constant after single and repeated administrations, and no accumulation of teduglutide was observed following repeated subcutaneous administrations. The total exposure of teduglutide increased proportionally with increasing dose levels on days 1 and 8, whereas peak plasma concentrations of teduglutide increased in a dose-proportional manner over the range of 10 to 50 mg. No gender-related difference was observed in the apparent clearance of teduglutide.

Peak plasma concentrations of teduglutide following subcutaneous administration of 20 mg as a 20-mg/mL formulation (cohort 3A) were approximately 78% higher than those observed for the 50-mg/mL formulation (cohort 3B). These data indicate that a less concentrated formulation of teduglutide results in a more rapid uptake and a slightly higher overall bioavailability of the peptide than the more concentrated formulation. A decreased frequency of injection site-related AEs was observed when subjects were administered a 50-mg/mL formulation of teduglutide as compared with that observed with a 20-mg/mL formulation. Because the drug is more rapidly taken up from the injection site following administration of the 20-mg/mL formulation, the higher incidence of injection site reactions with this formulation may be due more to volume of injection than the presence of drug.

Evaluations of AEs, clinical laboratory assessments, vital sign measurements, 12-lead ECGs, and physical examinations indicated that subcutaneous injections of 10 to 80 mg of teduglutide given by subcutaneous injection in the abdomen were safe and well tolerated. Overall, pharmacokinetic, safety, and tolerability results from the current study will help to determine optimal doses, formulations, and injected volume in future efficacy studies for the treatment of Crohn’s disease and other gastrointestinal indications.

Financial disclosure: David Wells and John Caminis are former employees of NPS and own stock in the company.

REFERENCES

3. Martin GR, Beck PL, Sigalet DL. Gut hormones, and short bowel syndrome: the enigmatic role of glucagon-like peptide-2 in the


