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Teduglutide

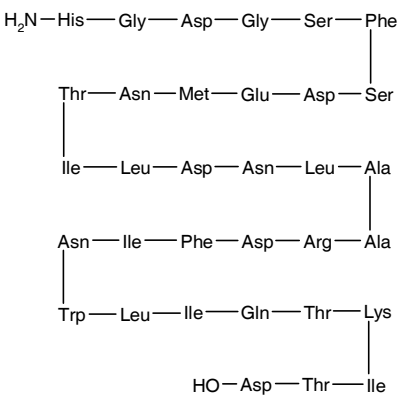
Rec INN; USAN

GLP-2 Receptor Agonist
Treatment of Short-Bowel Syndrome
Treatment of Crohn's Disease

ALX-0600
[Gly2]GLP-2

L-Histidyl-glycyl-L-aspartyl-glycyl-L-seryl-L-phenylalanyl-L-seryl-L-aspartyl-L-glutamyl-L-methionyl-L-asparaginyl-L-threonyl-L-isoleucyl-L-leucyl-L-aspartyl-L-asparaginyl-L-leucyl-L-alanyl-L-alanyl-L-arginyl-L-aspartyl-L-phenylalanyl-L-isoleucyl-L-asparaginyl-L-tryptophyl-L-leucyl-L-isoleucyl-L-glutaminyl-L-threonyl-L-lysyl-L-isoleucyl-L-threonyl-L-aspartic acid

[2-Glycine]-1-33-glucagon-like peptide II (human)



$C_{164}H_{252}N_{44}O_{55}S$
Mol wt: 3752.0852

CAS: 197922-42-2
EN: 246346

Abstract

Short-bowel syndrome (SDS) refers to the functional loss of large parts of the small intestine, causing malabsorption of nutrients and fluids, and malnutrition and dehydration if left untreated. Parenteral nutrition is used to manage the fluid and nutritional needs in patients with SDS, but the cost and the risk of complications have spurred the search for alternative therapies. Teduglutide (ALX-0600) is a metabolically stable analogue of the intestinal growth factor glucagon-like peptide-2 (GLP-2) that promotes mucosal growth and nutrient absorption in various animal models of SDS. In a phase II trial, teduglutide increased fluid and nutrient absorption in patients with SDS and it is currently in a phase III trial in patients with this syndrome. The agent also showed promise in a phase II study in patients with Crohn's disease.

Background

In healthy adults, the small intestine is typically 3-8 m in length, but in adults with short-bowel syndrome (SDS), the length of functional small intestine is usually < 0.2 m. The reduced intestinal area means that patients are less able to absorb nutrients and fluids, potentially leading to malnutrition and dehydration if left untreated. SBS is generally a result of surgical resection of the bowel, for example in patients with recurrent Crohn's disease, volvulus, mesenteric vascular complications or necrotizing enterocolitis; intestinal atresia in infants constitutes a congenital form of the disorder (1-4).

There is no cure for SDS and current therapies include provision of fluid and nutrients by parenteral nutrition and pharmacological agents to reduce diarrhea and gastric acid imbalances. Complications associated with long-term parenteral nutrition include liver and biliary tract complications, catheter-related infections, catheter occlusion and metabolic complications, prompting the search for alternative therapies. Intestinal transplantation has been used, but with mixed success (1, 2, 5).

SBS following surgery can be a temporary condition in some patients because the portion of the small intestine that remains is able to increase its absorptive capacity in compensation for the loss. The intestinal adaptation involves lengthening and enlargement of the intestinal villi, an increase in the diameter of the remaining intestine and reduced peristalsis to slow the rate of progress of the food. Mechanistically, this process is mediated by several gut hormones, including enteroglucagon, glucagon-like peptide-2 (GLP-2), epidermal growth factor (EGF), growth hormone (GH), cholecystokinin (CCK), gastrin, insulin and neurotensin (1, 2, 6-12; see also a compre-

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hensive web page provided by Dr. Drucker, http://www.glucagon.com/glp-2.htm).

GLP-2 was identified as an intestinotrophic agent a number of years ago and both animal and human studies have confirmed that GLP-2 plays an important role in regulating intestinal adaptation. However, the activity of GLP-2 itself is limited due to its rapid metabolism by dipeptidyl-peptidase IV (DPP-IV) (6, 13-17). Two strategies that have been employed in an attempt to increase the half-life of GLP-2 are enzymatic inhibition of DPP-IV and longer acting analogues of the hormone (13, 14, 18, 19).

Teduglutide (ALX-0600) is a GLP-2 analogue with an alanine-to-glycine amino acid substitution at position 2 which retains the activity of the parent compound in animal models and is resistant to DPP-IV degradation (1, 20). The agent is in phase III clinical trials for the treatment of patients with SDS and in phase II studies for the treatment of Crohn's disease, and it has been granted orphan drug status for SDS in the U.S. and the E.U.

Preclinical Pharmacology

Substitution of an alanine for a glycine at position 2 of GLP-2 to give teduglutide resulted in *in vitro* resistance to degradation by DPP-IV and reduced clearance in rats. Functionally, s.c. administration of teduglutide to rats led to an increased small intestinal weight, whereas native GLP-2 had no intestinotrophic effect due to its rapid clearance (20, 21). Using stably transfected BHK cells, the receptor binding and cAMP-stimulating activity of teduglutide was similar to parent compound, with respective IC_{50} values for high-affinity sites of 4.8 and 2.2 pM, respective values for low-affinity sites of 42.9 and 49.2 nM, and respective values for cAMP generation of 9.2 and 14.0 nM (22).

Reduced metabolism was also demonstrated in pigs, where the t_{max} for native GLP-2 was 10 min and the plasma half-life was 7.5 min following i.v. infusion. The t_{max} of teduglutide was similar, but the half-life was 2.5 times greater (17.4 min), consistent with its increased resistance to the enzyme DPP-IV (23).

Using HEK293 cells stably expressing the human GLP-2 receptor, teduglutide was found to potently displace [^{125}I]-[Tyr34]-hGLP-2 from high-affinity (K_i = 20 pM) and low-affinity binding sites (K_i = 85 nM), and to stimulate adenylyl cyclase activity (EC_{50} = 0.5 nM). *In vivo*, administration of teduglutide (0.25 mg/kg/day by twice-daily s.c. injection for 14 days) to rats caused a 50% increase in total small intestinal weight and pronounced increases in cell proliferative activity in the duodenum and jejunum (24).

In other experiments, HEK293 cells expressing the human GLP-2 receptor were exposed to different concentrations of teduglutide, followed by a washout period and re-challenge. When cells that had been preincubated at either 0.01 or 1 μM teduglutide for 1 h were re-challenged with > 0.01 μM teduglutide, cAMP accumulation was attenuated. However, if the re-challenge concentration was < 0.01 μM, cAMP production increased, indicating receptor modulation following exposure to teduglutide (25).

The intestinotrophic properties of teduglutide were studied *in vitro* using isolated rat intestinal mucosal cells. Exposure to 10 pM teduglutide produced a maximal cAMP response (268%), which was reduced or completely abolished by pretreatment with > 1 nM teduglutide, indicating receptor desensitization. Teduglutide stimulated a modest proliferative response (128% of control) that was dependent on the activity of the protein kinase A (PKA) signaling pathway. No changes in p44/p42 MAPK (mitogen-activated protein kinase) phosphorylation or in the levels of cytosolic calcium were detected in these cells upon exposure to teduglutide (26).

In CD-1 mice, teduglutide (0.025-1.0 mg/kg/day once or twice daily s.c. for up to 28 days) increased the weight and length of the small intestine, and to a lesser extent the colon (estimated ED_{50} = 0.065 mg/kg/day), in a time- and dose-dependent fashion, reaching a plateau within 2 weeks of treatment initiation; once- and twice-daily dosing produced similar effects. An increase in mucosal protein and DNA content was also seen. The intestinotrophic effect of teduglutide was fully reversible, returning to baseline levels 10 days after cessation of treatment (27, 28).

The combination of teduglutide with other intestinotrophic growth factors, *i.e.*, insulin-like growth factors-I and -II (IGF-I and -II), EGF and hGH, was also investigated in mice. Teduglutide alone (2.5 μg s.c. twice daily) caused increases in large and small bowel mass and increased the crypt depth and villus height. Co-administration of teduglutide with either hGH, IGF-I or a combination of all five growth factors led to further increases in intestinal growth (29).

The antiapoptotic effect of teduglutide was investigated in CD-1 mice injected with saline or 50 ng/kg-500 μg/kg teduglutide. Phosphorylation of protein kinase B (PKB) increased 12-fold at the dose of 50 μg/kg and reached a maximum within 30 min of injection. There was also a 1.7-fold decrease in the cleavage of caspase-3 to its active proapoptotic form. These results imply teduglutide signaling through the PKB/Akt pathway to promote cell survival in small intestinal epithelium (30).

Teduglutide reduced rat colon contractility with an IC_{50} of 4.9 nM (compared with 13.5 nM for native GLP-2) in an *ex vivo* model of gastric emptying. Upon re-challenge of the rat colon muscle strips after a washout period, the contractile response to teduglutide was reduced, indicating GLP-2 receptor desensitization (31).

Experiments in jejunal segments from CD-1 mice demonstrated the ability of teduglutide to improve intestinal epithelial barrier function via both the para- and transcellular pathways (32-34).

Teduglutide administered chronically to rats (1 μg/g s.c. twice daily for 10 days) had no effect on the diurnal increase in SGLT1, GLUT1 or GLUT5 mRNA expression but increased SGLT1 protein levels, particularly in apical membranes (35).

Following removal of 75% of the mid-jejuno-ileum in rats, administration of teduglutide (0.1 μg/g s.c.) twice

daily for 6-21 days induced mucosal hyperplasia in the proximal jejunum and restored intestinal absorption, indicating that it can enhance the intestinal adaptive response to massive resection (36).

In another study, removal of 60% of the distal small intestine in rats was followed by treatment with vehicle or teduglutide (50 μg s.c. twice daily for 2 weeks). Teduglutide increased small intestinal weight to 174% compared to vehicle-treated resected rats and increased mucosal area in the proximal and mid-parts of the small intestine. In a subgroup of treated animals that were left for 4 weeks without further treatment, both the small intestinal weight and mucosal area returned to levels comparable to vehicle-treated controls, indicating that the intestinotrophic effect of teduglutide is reversible upon cessation of treatment (37).

Following 90% resection of the proximal small bowel in male Lewis rats, the animals were treated with a number of intestinotrophic growth factors for 14 days. Sham-resected animals (intestinal transection without removal of intestinal material and treated with vehicle alone) had gained 6.6% of their initial weight, whereas resected animals that had been treated with vehicle alone lost 6.2% of their weight. The resected animals treated with GH or IGF-I gained 9.9% and 6.0% of their initial weight, and teduglutide-treated animals retained their initial weight. All three growth factor treatments were associated with variable increases in villus height and normalization of net glucose flux (38).

To investigate the molecular mechanisms underlying intestinal adaptation in response to teduglutide and other growth factors, epithelial IEC-18 cell cultures were exposed to IGF-I, EGF, bFGF, nerve growth factor (NGF) or teduglutide. EGF, bFGF and teduglutide, but not IGF-I or NGF, increased the mRNA levels of the immediate early gene *PC4/TIS7*. Administration of teduglutide to mice caused an increase in *PC4/TIS7* mRNA levels in the small bowel, indicating that this gene possibly plays a role in coordinating the response of several intestinotrophic growth factors in the intestinal adaptive response (39).

In a murine model of dextran sulfate-induced colitis, co-administration of teduglutide for 10 days prevented weight loss (20-25% weight loss in dextran sulfate + vehicle-treated animals), reduced the expression of the inflammatory marker IL-1, increased colon length, increased crypt depth and enhanced mucosal area and integrity (40, 41).

Teduglutide (0.1 μg s.c. twice daily for 3 days following treatment with 5-fluorouracil [5-FU]) reversed the chemotherapy-induced loss of jejunal wet weight, villus height and crypt depth in a rat model of chemotherapy-induced enteritis. Administration of teduglutide prior to chemotherapy was less beneficial (42).

The optimal dosing regimen of teduglutide was further explored in the 5-FU-induced enteritis model. In this study, teduglutide was administered at doses of 15-270 nmol/kg for 3 or 7 days before 5-FU, together with 5-FU, for 3 days before and together with 5-FU, and for 3 days before, together with and for 3 days after 5-FU. When administered for 7 days prior to 5-FU, teduglutide (90 and 270 nmol/kg) significantly increased the small intestine/body weight ratio compared to 5-FU-treated animals; administration prior to and concomitant with 5-FU (15-270 nmol/kg) resulted in significant increases in small intestine/body weight ratios and a significant reduction in body weight loss, and administration prior to, concurrent with and following 5-FU (30-270 nmol/kg) significantly increased small intestine/body weight ratios (43).

In vitro, teduglutide protected BHK cells stably expressing the rat GLP-2 receptor from the apoptotic effect of the topoisomerase I inhibitor irinotecan. Teduglutide blocked the activation of caspase-8 and -3 and reduced poly(ADP-ribose) polymerase (PARP) cleavage in these cells. When mice were administered 5-FU or irinotecan with or without teduglutide, the growth factor prevented epithelial injury and crypt apoptosis, reduced bacteremia and improved survival. In tumor-bearing mice, teduglutide reversed the toxic effect of irinotecan on the intestine but did not alter the antitumor efficacy of the chemotherapy. It was concluded that the antiapoptotic effect of teduglutide may be useful for attenuating intestinal mucositis in patients undergoing chemotherapy (44).

Using a mouse model of experimental enteritis induced by whole-body gamma irradiation, teduglutide (0.2 mg/kg/day s.c.) twice daily for 6 or 14 days prior to irradiation protected crypt stem cells from the damaging effects of radiation (mean protection factor of 1.3-1.5). This effect was only observed when teduglutide was administered prior to radiation (mean protection factor of 0.86 when teduglutide was administered for 4 days post-irradiation). These results provide further support for the potential of teduglutide for protecting against mucositis associated with cancer therapy (45, 46).

However, a possible cancer-promoting effect of teduglutide was highlighted in a study in mice bearing colonic neoplasms. The methylating agent 1,2-dimethylhydrazine was used to induce colonic tumors in mice and following a treatment-free interval of 2 or 3 months, mice were treated with teduglutide (25 μg s.c. twice daily) or vehicle alone for a further 10 days or 1 month. Teduglutide treatment did not affect survival, but did cause an increase in the tumor load, indicating the need for further experimentation in this area (47).

In a mouse model of nonsteroidal antiinflammatory drug (NSAID)-induced enteritis, induction of mucosal injury by indomethacin (7 mg/kg injected twice) caused 50% mortality, whereas pre-, co- or post-treatment with teduglutide reduced the indomethacin-induced mortality (> 90% survival with pretreatment). Intestinal inflammation, intestinal ulceration and bacteremia in the surviving mice were also reduced, accounting for the increased survival. These actions were associated with increased epithelial and crypt cell proliferation, reduced crypt cell apoptosis and reduced intestinal permeability (48).

Teduglutide treatment (0.1 mg/kg s.c. twice daily for 3 days) also reduced intestinal permeability in a rat model of acute necrotizing pancreatitis. This was associated

with a 20-30% decrease in translocation of Gram-negative microorganisms to the mesenteric lymph nodes, the pancreas and the peritoneum relative to saline-treated controls. The severity of pancreatitis was unaffected, suggesting that teduglutide might have a beneficial effect as an adjuvant for treating compromised intestinal permeability in patients with this condition (49).

Pharmacokinetics and Metabolism

Thirty-two healthy male volunteers were randomized to receive a single s.c. injection of teduglutide at doses of 2.5, 5.0, 7.0 or 10 mg or placebo. Pharmacokinetics were proportional to dose. Mean peak plasma levels were 27-101 ng/ml and were reached at about 3 h (50).

Safety

In the above study, teduglutide was safe and well tolerated. Six adverse events, *i.e.*, 5 cases of injection-site reactions (pain and pruritus/erythema) and 1 case of rash, were considered to be related to drug, all in the two higher dose groups and all mild. Headache was reported by 3 subjects, but appeared to be related to fasting (50).

Clinical Studies

The efficacy of teduglutide was investigated in an open-label pilot study in 17 patients with SBS due to extensive surgical resection of the small bowel. For dosing and subsequent analysis, patients were subdivided into two groups: those with end-jejunostomy and no colon in continuity received teduglutide doses of 0.03, 0.1 or 0.15 mg/kg/day s.c. once or twice daily for 21 days (n=10 in the final analysis), and patients with at least 50% colon in continuity received a once-daily dose of 0.1 mg/kg teduglutide for 21 days (n=5 in the final analysis). The drug was well tolerated and the most commonly reported adverse events were swelling of jejunostomy nipple (7/10), lower limb edema (7/16), headache (4/16) and abdominal pain (3/16). At the end of the 3-week treatment period, intestinal absorption was improved in both groups. Improvements were demonstrated by increased fluid absorption (increased by 22%), increased electrolyte absorption (urine sodium excretion increased by 53 mmol/day) and moderately improved nutrient uptake (fecal energy excretion reduced by 808 kJ/day). In the end-jejunostomy patients, improved nutritional uptake was paralleled by hyperplasia in the epithelial lining of the remaining jejunum: villus height increased by 38%, crypt depth increased by 22% and the mitotic index increased by 115%. These changes were not seen in the colon of patients with at least 50% colon in continuity. Three weeks after the cessation of treatment, these changes in intestinal absorption and histology had reversed (13, 51-53). Based on the results of this trial, a randomized, placebo-controlled phase III trial of teduglutide in adults with parenteral nutrition-dependent SBS was initiated (protocol CL0600-004) (54). The primary endpoint in this trial is a reduction in the use of parenteral nutrition following a 6-month dosing period of once-daily teduglutide at either 0.05 or 0.1 mg/kg/day A 6-month extension to protocol CL0600-004 is also under way (55).

Teduglutide has also been investigated in patients with moderate to severe Crohn's disease (protocol CL0600-008). In this double-blind phase II trial, 100 patients were randomized to one of three active treatment groups (teduglutide 0.05, 0.1 or 0.2 mg/kg/day) or placebo, self-administered as a daily s.c. injection for 8 weeks. Teduglutide was well tolerated. Adverse events were mild and included abdominal pain and injection-site reactions. The primary endpoint, complete remission at week 8 (Crohn's Disease Activity Index [CDAI] score = 150 or less), was achieved by 56% of patients in the 0.2 mg/kg/day group compared to 33% of patients on placebo (56, 57). In an open-label extension to this study, all patients received 0.1 mg/kg/day for a further 12 weeks (protocol CL0600-009). At the end of this period (week 20), 63% of those on the initial dose of 0.2 mg/kg/day were in remission (*vs.* 25% on placebo), and patients in this group were most likely to maintain remission (56% remission at week 24 *vs.* 10% remission in those initiating on placebo). There were no serious adverse events, and the most frequent adverse event was injection-site reactions (58, 59).

Source

NPS Pharmaceuticals (US).

References

1. Ferrone, M., Scolapio, J.S. *Teduglutide for the treatment of short bowel syndrome*. Ann Pharmacother 2006, 40(6): 1105-19.

2. DeLegge, M., Alsolaiman, M.M., Barbour, E., Bassas, S., Siddiqi, M.F., Moore, N.M. *Short bowel syndrome: Parenteral nutrition versus intestinal transplantation. Where are we today?* Dig Dis Sci 2007, 52(4): 876-92.

3. Slater, G., Aufses, A.H. Jr. *Small-bowel length in Crohn's disease*. Am J Gastroenterol 1991, 86(8): 1037-40.

4. Nightingale, J.M.D., Bartram, C.I., Lennard-Jones, J.E. *Length of residual small bowel after partial resection: Correlation between radiographic and surgical measurements*. Gastrointest Radiol 1991, 16(4): 305-6.

5. *AGA Medical Position Statement. Short bowel syndrome and intestinal transplantation*. Gastroenterology 2003, 124: 1105-10.

6. Martin, G.R., Beck, P.L., Sigalet, D.L. *Gut hormones, and short bowel syndrome: The enigmatic role of glucagon-like peptide-2 in the regulation of intestinal adaptation*. World J Gastroenterol 2006, 12(26): 4117-29.

7. Doldi, S.B. *Intestinal adaptation following jejuno-ileal bypass*. Clin Nutr 1991, 10(3): 138-45.

8. Dowling, R.H., Booth, C.C. *Functional compensation after small bowel resection in man*. Lancet 1966, 2: 146-7.

9. Weinstein, L.D., Shoemaker, C.P., Hersh, T., Wright, H.K. *Enhanced intestinal absorption after small bowel resection in man*. Arch Surg 1968, 99(5): 560-2.

10. Sham, J., Martin, G., Meddings, J.B., Sigalet, D.L. *Epidermal growth factor improves nutrition outcome in a rat model of short bowel syndrome*. J Pediatr Surg 2002, 37(5): 765-9.

11. Kurkchubasche, A.G., Rowe, M.I., Smith, S.D. *Adaptation in short-bowel syndrome: Reassessing old limits*. J Pediatr Surg 1993, 28(8): 1069.

12. Podolsky, D.K. *Regulation of intestinal epithelial proliferation: A few answers, many questions*. Am J Physiol 1993, 264(2, Part 1): G179-86.

13. Jeppesen, P.B. *Glucagon-like peptide-2: Update of the recent clinical trials*. Gastroenterology 2006, 130(2, Suppl. 1): S127-31.

14. Wallis, K., Walters, J.R., Forbes, A. *Review article: Glucagon-like peptide 2 — Current applications and future directions*. Aliment Pharmacol Ther 2007, 25(4): 365-72.

15. Drucker, D.J., Ehrlich, P., Asa, S.L., Brubaker, P.L. *Induction of intestinal epithelial proliferation by glucagon-like peptide 2*. Proc Natl Acad Sci USA 1996, 93(15): 7911-6.

16. Lovshin, J., Drucker, D.J. *New frontiers in the biology of GLP-2*. Regul Pept 2000, 90(1-3): 27-32.

17. Tavares, W., Drucker, D.J., Brubaker, P.L. *Enzymatic- and renal-dependent catabolism of the intestinotrophic hormone glucagon-like peptide-2 in rats*. Am J Physiol Endocrinol Metab 2000, 278(1): E134-9.

18. Hartmann, B., Thulesen, J., Kissow, H. et al. *Dipeptidyl peptidase IV inhibition enhances the intestinotrophic effect of glucagon-like peptide-2 in rats and mice*. Endocrinology 2000, 141(11): 4013-20.

19. Drucker, D.J. *Glucagon-like peptide 2*. Trends Endocrinol Metab 1999, 10: 153-6.

20. Drucker, D.J., Shi, Q., Crivici, A. et al. *Regulation of the biological activity of glucagon-like peptide 2 in vivo by dipeptidyl peptidase IV*. Nat Biotechnol 1997, 15(7): 673-7.

21. Brubaker, P.L., Crivici, A., Izzo, A., Ehrlich, P., Tsai, C.H., Drucker, D.J. *Circulating and tissue forms of the intestinal growth factor, glucagon-like peptide-2*. Endocrinology 1997, 138(11): 4837-43.

22. DaCambra, M.P., Yusta, B., Sumner-Smith, M., Crivici, A., Drucker, D.J., Brubaker, P.L. *Structural determinants for activity of glucagon-like peptide-2*. Biochemistry 2000, 39(30): 8888-94.

23. Hare, K.J., Hartmann, B., Deacon, C.F., Holst, J.J. *In vivo degradation of glucagon-like peptide 2 (GLP-2) and Gly2-GLP-2*. Dig Dis Week (May 17-22, Orlando) 2003, Abst M913.

24. Demchyshyn, L.L., Colantonio, C.M., Liao, L., Burrowes, C., Yang, Z.J. *ALX-0600: A potent glucagon-like peptide-2 receptor agonist*. Dig Dis Week (May 20-23, Atlanta) 2001, Abst 2589.

25. Maclean, N.A., Yu, M., Demchyshyn, L.L. *Homologous desensitization of the human glucagon-like peptide-2 receptor in HEK293 cells*. Dig Dis Week (May 19-22, San Francisco) 2002, Abst T918.

26. Walsh, N.A., Yusta, B., DaCambra, M.P., Anini, Y., Drucker, D.J., Brubaker, P.L. *Glucagon-like peptide-2 receptor activation in the rat intestinal mucosa*. Endocrinology 2003, 144(10): 4385-92.

27. Yang, Z.J., Burrowes, C., Urlando, C., Crivici, A., Lee, D.K.H. *Characterization of the intestinotrophic effect of a glucagon-like peptide 2 (GLP-2) analogue in mice*. FASEB J 1999, 13(5, Part 2): Abst 626.3.

28. Yang, Z.J., Burrowes, C., Urlando, C., Demchyshyn, L.L. *The intestinotrophic properties of ALX-0600, a glucagon-like peptide-2 analogue*. Dig Dis Week (May 21-24, San Diego) 2000, Abst 2880.

29. Drucker, D.J., DeForest, L., Brubaker, P.L. *Intestinal response to growth factors administered alone or in combination with human [Gly2]glucagon-like peptide 2*. Am J Physiol – Gastrointest Liver Physiol 1997, 273(6): G1252-62.

30. Dube, P.E., Brubaker, P.L. *Glucagon-like peptide-2 acutely activates PKB/Akt and decreases apoptotic signaling in the mouse small intestinal epithelium*. Dig Dis Week (May 14-19, Chicago) 2005, Abst S1295.

31. Wang, H., Demchyshyn, L.L. *Teduglutide (ALX-0600), a glucagon-like peptide-2 (GLP-2) analogue inhibits contractility in the colon ex vivo*. Gastroenterology [Dig Dis Week (May 20-25, Los Angeles) 2006] 2006, 130(4, Suppl, 2): Abst W1605.

32. Benjamin, M.A., Yang, P.C., McKay, D.M. *Chronic administration of glucagon-like peptide-2 (GLP-2) alters murine intestinal enterocyte from and function*. Dig Dis Week (May 16-19, Orlando) 1999, Abst 2868.

33. Benjamin, M.A., McKay, D.M., Yang, P.C., Cameron, H., Perdue, M.H. *Glucagon-like peptide-2 enhances intestinal epithelial barrier function of both transcellular and paracellular pathways in the mouse*. Gut 2000, 47(1): 112-9.

34. Benjamin, M.A., McKay, D.M., Perdue, M.H. *Glucagon-like peptide-2 (GLP-2) reduces intestinal epithelial permeability of both the paracellular and transcellular pathway*. Dig Dis Week (May 17-20, New Orleans) 1998, Abst 4620.

35. Ramsanahie, A.P., Berger, U.V., Zinner, M.J., Whang, E.E., Rhoads, D.B., Ashley, S.W. *Effect of glucagon-like peptide-2 (GLP-2) on diurnal SGLT1 expression*. Dig Dis Sci 2004, 49(11-12): 1731-7.

36. Scott, R.B., Kirk, D., MacNaughton, W.K., Meddings, J.B. *GLP-2 augments the adaptive response to massive intestinal resection in rat*. Dig Dis Week (May 17-20, New Orleans) 1998, Abst 3722.

37. Hartmann, B., Hare, K.J., Kissow, H., Thulessen, J., Poulsen, S.S., Holst, J.J. *GLP-2 induces additional, but reversible, intestinal growth in rats adapted to intestinal resection*. Dig Dis Week (May 17-22, Orlando) 2003, Abst M912.

38. Sigalet, D.L., Martin, G.R. *Hormonal therapy for short bowel syndrome*. J Pediatr Surg 2000, 35(2): 360-3.

39. Swietlicki, E., Iordanov, H., Fritsch, C., Yi, L., Levin, M.S., Rubin, D.C. *Growth factor regulation of PC4/TIS7, an immediate early gene expressed during gut adaptation after resection*. JPEN J Parenter Enteral Nutr 2003, 27(2): 123-31.

40. Drucker, D.J., Yusta, B., Boushey, R.P., DeForest, L., Brubaker, P.L. *Human [Gly2]GLP-2 reduces the severity of colonic injury in a murine model of experimental colitis*. Am J Physiol – Gastrointest Liver Physiol 1999, 276(1): G79-91.

41. Drucker, D.J., DeForest, L., Yusta, B., Brubaker, P.L. *Enhancement of intestinal epithelial repair by a human glucagon-like peptide-2 analogue, h[Gly2]-GLP-2, in a murine model of ulcerative colitis*. Gastroenterology 1998, 114(4, Part 2): Abst G3968.

42. Tavakkolizadeh, A., Shen, R., Abraham, P. et al. *Glucagon-like peptide 2: A new treatment for chemotherapy-induced enteritis*. J Surg Res 2000, 91(1): 77-82.

43. Petersen, Y.M., Larsen, B.D., Petersen, J.S. *Administration of the protease-resistant glucagon-like peptide 2 analog, [GLY2]GLP-2, prior to and concurrently with the chemotherapeutic agent, 5-fluorouracil, inhibits small intestinal atrophy and attenuates bodyweight loss in mice*. Gastroenterology [Dig Dis Week (May 14-19, Chicago) 2005] 2005, 128(4, Suppl. 2): Abst S1297.

44. Boushey, R.P., Yusta, B., Drucker, D.J. *Glucagon-like peptide (GLP)-2 reduces chemotherapy-associated mortality and enhances cell survival in cells expressing a transfected GLP-2 receptor*. Cancer Res 2001, 61(2): 687-93.

45. Booth, C., Booth, D., Williamson, S., Demchyshyn, L.L., Potten, C.S. *Teduglutide ([Gly2]GLP-2) protects small intestinal stem cells from radiation damage*. Cell Prolif 2004, 37(6): 385-400.

46. Potten, C.S., Williamson, S., Demchyshyn, L.L., Booth, C. *ALX-0600, a glucagon-like peptide-2 analogue, protects small intestinal stem cells from radiation damage*. Dig Dis Week (May 17-22, Orlando) 2003, Abst W998.

47. Thulesen, J., Hartmann, B., Hare, K.J. et al. *Glucagon-like peptide 2 (GLP-2) accelerates the growth of colonic neoplasms in mice*. Gut 2004, 53(8): 1145-50.

34. Boushey, R.P., Yusta, B., Drucker, D.J. *Glucagon-like peptide 2 decreases mortality and reduces the severity of indomethacin-induced murine enteritis*. Am J Physiol Endocrinol Metab 1999, 277(5): E937-47.

49. Kouris, G.J., Liu, Q., Rossi, H. et al. *The effect of glucagon-like peptide 2 on intestinal permeability and bacterial translocation in acute necrotizing pancreatitis*. Am J Surg 2001, 181(6): 571-5.

50. Metcalfe, A.J., Oliver, S.D., Dietrich, J. *An evaluation of single dose administration of ALX-0600, a GLP-2 analog, in healthy male subjects*. Gastroenterology [Dig Dis Week (May 24, San Diego) 2000] 2000, 118(4, Suppl. 2, Part 2): Abst 4973.

51. Jeppesen, P.B., Sanguinetti, E.L., Buchman, A. et al. *Teduglutide (ALX-0600), a dipeptidyl peptidase IV resistant glucagon-like peptide 2 analogue, improves intestinal function in short bowel syndrome patients*. Gut 2005, 54(9): 1224-31.

52. Tappenden, K.A., Bartholeme, A.L., Demchyshyn, L.L. et al. *ALX-0600, a glucagon-like peptide-2 (GLP-2) analog, enhances intestinal structure and function in patients with short bowel syndrome (SBS)*. Dig Dis Week (May 19-22, San Francisco) 2002, Abst S1250.

53. Jeppsen, P.B., Blosch, C., Lopansri, J. et al. *ALX-0600, a dipeptidyl peptidase-IV resistant glucagon-like peptide-2 (GLP-2) analog, improves intestinal function in short bowel syndrome (SBS) patients with jejunostomy*. Dig Dis Week (May 19-22, San Francisco) 2002, Abst S1249.

54. *Safety and efficacy study of teduglutide in subjects with short bowel syndrome (NCT00081458)*. ClinicalTrials.gov Web site, June 18, 2007.

55. *Safety and efficacy study of teduglutide in subjects with short bowel syndrome who completed protocol CL0600-004 (NCT00172185)*. ClinicalTrials.gov Web site, June 18, 2007.

56. *Safety and efficacy of ALX-0600 in subjects with active Crohn's disease (NCT00072839)*. ClinicalTrials.gov Web site, June 18, 2007.

57. Buchman, A., Katz, S., Shnaidman, M., Jacobs, D.O. *Effect of teduglutide on patients with moderate-severe Crohn's disease after 8 weeks of therapy: A prospective double-blind, placebo controlled trial*. Gastroenterology [Dig Dis Week (May 20-25, Los Angeles) 2006] 2006, 131(3): 949-50.

58. *Safety and efficacy of ALX-0600 in subjects with active Crohn's disease who completed protocol CL0600-008 (NCT00308438)*. ClinicalTrials.gov Web site, June 18, 2007.

59. Buchman, A., Katz, S., Shnaidman, M., Jacobs, D.O. *Effect of teduglutide in patients with moderate-severe Crohn's disease after 20 weeks of daily therapy*. Am J Gastroenterol [71st Annu Sci Meet Am Coll Gastroenterol (Oct 20-25, Las Vegas) 2006] 2006, 101(Suppl. 2): Abst 1190.