

Liraglutide (NN2211) – Enters Phase 2 Clinical Trials

Currently in phase 2 clinical trials, liraglutide is based on a naturally occurring hormone called Glucagon-Like Peptide-1 (GLP-1). Studies to date suggest liraglutide improves control of blood glucose (glycemic control) and may have advantages over current therapies:

- ? It acts in a glucose-dependent manner, meaning that it will stimulate insulin secretion only when blood glucose levels are higher than normal
- ? It has the potential for beta cell regeneration (seen in animal studies)
- ? It shows negligible risk of hypoglycemia, and only mild and transient side effects
- ? It decreases appetite and maintains body weight
- ? It is suitable for once-daily administration

Glucagon-Like Peptide-1

Liraglutide is a long-acting derivative of GLP-1, a naturally occurring peptide hormone discovered in the early nineteen eighties. Physiologically, GLP-1 is released from the GI tract upon ingestion of food. GLP-1 has four main mechanisms of action which all work in a glucose-dependent manner:

- ? It promotes the synthesis and release of insulin from the pancreas
- ? It lowers blood levels of glucagon, a hormone that normally stimulates glucose production and release from the liver
- ? It promotes feelings of satiety by slowing gastric emptying, which attenuates blood glucose surges following meals and decreases food intake
- ? It inhibits death of insulin-producing pancreatic beta cells as well as stimulating growth, proliferation and neogenesis
- ? The glucose-dependent activity (affecting both types 1 and 2) is important because it results in GLP-1 being more active when blood glucose is elevated, but being less active when blood glucose is normal or low. Thus, GLP-1 does not cause serious hypoglycaemia even at high doses.ⁱⁱ

Liraglutide (NN2211)

Liraglutide is the first once-daily GLP-1 derivative in development for the treatment of type 2 diabetes. GLP-1, in its natural form, is short-lived in the body (the half-life after subcutaneous injection is approximately 1 hour), so it is not very useful as a therapeutic agent. However, liraglutide

is a 'timed release' form of GLP-1 with prolonged activity; the half-life after subcutaneous injection is 11–15 hours, making it suitable for once-daily dosing.^{iii,iv}

The prolonged action of liraglutide is achieved by attaching a fatty acid molecule at one position of the GLP-1 molecule, enabling it to bind to albumin within the subcutaneous tissue and bloodstream. The active GLP-1 is then released from albumin at a slow, consistent rate. Binding with albumin also results in slower degradation and reduced elimination of liraglutide from the circulation by the kidneys compared to GLP-1 in its natural form.

To date, liraglutide has been studied in animals and in humans, and is currently in phase 2 clinical trials. Some of the key findings include:

In men with type 2 diabetes, liraglutide effectively reduced fasting as well as meal-related glycaemia (12 hours after liraglutide administration) by increasing insulin secretion, delaying gastric emptying, and suppressing prandial glucagon secretion.^v

In a study of 190 people with type 2 diabetes, those who took liraglutide maintained weight, whereas those who took the insulin secretagogue glimepiride gained weight as expected. The main side effects were gastrointestinal, and mild and transient; the risk of hypoglycaemia was very low^{vi}

Liraglutide has also been shown to reduce food intake and promote weight loss in obese monkeys^{vii} and other diabetic and/or obese animal models.^{viii,ix,x,xi} It has also been shown to reduce blood triglyceride levels in normal, obese and prediabetic rats^{12,xii}

Studies in diabetic rats and mice show that liraglutide increases beta cell mass^{13,xiii,xiv} and reduces the death of beta cells (apoptosis or programmed cell death)^{xv,xvi} Liraglutide is a promising GLP-1 derivative in development for treatment of type 2 diabetes. Its multiple modes of action offer potential advantages over many current therapies. Studies in humans show it can improve glycaemic control, decrease appetite and maintain body weight, with minimal side effects. Its glucose-dependent stimulation of insulin secretion and inhibition of glucagon appear to improve glycaemic control while minimising the risk of hypoglycaemia. Studies in animals further suggest that liraglutide can inhibit beta cell death and stimulate their growth as well as lower blood triglyceride levels.

It is anticipated that this new drug could be brought to market in 2006.

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ⁱⁱ Vilsbøll T, Krarup T, Madsbad S, Holst JJ. No reactive hypoglycemia in type 2 diabetic patients after subcutaneous administration of GLP-1. *Diabetic Medicine* 2001; 18: 144-149.

ⁱⁱⁱ Agerso H, Jensen LB, Elbrønd B, Rolan P, Zdravkovic M. The pharmacokinetics, pharmacodynamics, safety and tolerability of NN2211, a new long-acting GLP-1 derivative, in healthy men. *Diabetologia* 2002; 45:195-202.

^{iv} Bodil Elbrønd B, Jakobsen G, Larsen S, et al. Pharmacokinetics, pharmacodynamics, safety, and tolerability of a single-dose of NN2211, a long-acting glucagon-like peptide 1 derivative, in healthy male subjects. *Diabetes Care* 2002; 25:1398–1404.

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- ^v Juhl CH, Hollingdal M, Sturis J, et al. Bedtime administration of NN2211, a long-acting GLP-1 derivative, substantially reduces fasting and postprandial glycemia in Type 2 diabetes. *Diabetes* 2002; 51:424- 9.
- ^{vi} Matthews S, Schmitz MO, Langendorf KW, Jakobsen G. A long-acting GLP-1 derivative, NN2211: its use in the treatment of type 2 diabetes. Poster 678. Presented at: European Association for the Study of Diabetes annual meeting, Budapest, Hungary, September, 2002.
- ^{vii} Hansen BC, Bjenning C, Knudsen LB. Sustained appetite suppression and weight loss in obese rhesus monkeys treated with a long-acting GLP-1 derivative, NN2211. Poster 751. Presented at: European Association for the Study of Diabetes annual meeting. Glasgow, Scotland, September 2001.
- ^{viii} Bjenning C, Romer J, Knudsen LB. NN2211, a Novo Nordisk GLP-1 derivate, suppresses appetite in wild type but not in GLP-1r^{-/-} mice. Poster 751. Presented at: North American Association for the Study of Obesity annual meeting. Quebec City, Canada, October 10, 2001.
- ^{ix} Larsen PJ, Fledelius C, Knudsen LB, Tang-Christensen M. Systemic administration of the long-acting GLP-1 derivative NN2211 induces lasting and reversible weight loss in both normal and obese rats. *Diabetes* 2001; 50:2530–2539.
- ^x Rolin B, Larsen MO, Gotfredsen CF. The long-acting GLP-1 derivative NN2211 ameliorates glycemia and increases β -cell mass in diabetic mice. *Am J Physiol Endocrinol Metab* 2002; 283:E745–E752.
- ^{xi} Bentzen L, Wei L, Lange KZ, Knudsen LB. The long-acting GLP-1 derivative NN2211 improves glucose tolerance and normalizes body weight in diet induced obese rats. Poster 665. Presented at: European Association for the Study of Diabetes annual meeting, Budapest, Hungary, September 2002.
- ^{xii} Rolin B, Gotfredsen C, Sturis J, et al. NN2211, a long-acting GLP-1 derivative, ameliorates glycaemia and reduces triglyceride levels in pre-diabetic ZDF rats. Poster 1294. Presented at: American Diabetes Association annual meeting. Philadelphia, Pennsylvania, June 2001.
- ^{xiii} Sturis J et al. Long-acting GLP-1 derivative NN2211 markedly attenuates diabetes development in the male Zucker diabetic fatty rat. Poster 559. Presented at: European Association for the Study of Diabetes annual meeting, Jerusalem, Israel, September 2000.
- ^{xiv} Gotfredsen C, et al. [The GLP-1 derivative NN2211 inhibits cytokine-induced apoptosis, in primary rat \$\beta\$ -cells](#). *Diabetes* 2001; 50 (Suppl 2):A31 (126-OR).
- ^{xv} Bregenholt S, Moldrup A, Knudsen LB, Petersen JS. The GLP-1 derivative NN2211 inhibits cytokine-induced apoptosis in primary rat β -cells, oral presentation 125-OR at the ADA 61st Scientific Sessions, Philadelphia, USA, June 2001.
- ^{xvi} Bregenholt S, Møldrup A, Blume N, Knudsen LB, Petersen JS. The GLP-1 analogue, NN2211, inhibits free fatty acid-induced apoptosis in primary rat β -cells. Oral presentation, abstract 65. Presented at: European Association for the Study of Diabetes annual meeting, Glasgow, Scotland, September 2001.