Drugs of the Future 2002, 27(7): 645-647

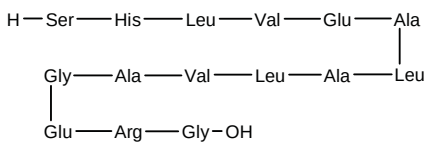
CCC: 0377-8282/2002

NBI-6024

Antidiabetic

H-L-Ser-L-His-L-Leu-L-Val-L-Glu-L-Ala-L-Leu-L-Ala-L-Leu-L-Val-L-Ala-Gly-L-Glu-L-Arg-Gly-OH

[16B-L-Alanine,19B-L-alanine]insulin(human) chain B (9-23) peptide



$C_{66}H_{112}N_{20}O_{21}$

Mol wt: 1521.73

CAS: 239480-61-6

EN: 273845

Abstract

Type 1 diabetes mellitus is characterized by autoimmune destruction of pancreatic beta-cells resulting in the inability of the pancreas to produce insulin and consequent hyperglycemia. To date, the standard therapy available for management of type 1 diabetes is daily insulin injections to control blood glucose levels. However, insulin therapy is not a solution for natural disease progression or prevention and, if incorrectly administered, it may be accompanied by life-threatening complications. Thus, research has focused on the search for therapies which can both manage and prevent type 1 diabetes onset. NBI-6024 is a diabetes vaccine that is composed of an altered peptide ligand (APL) which is a dominant pancreatic antigen engineered so that it no longer can be recognized by autoreactive immune cells. Because APL has been shown to downregulate immune-mediated destructive processes and reduce the incidence of diabetes in preclinical models, NBI-6024 was chosen for further clinical development. To date, NBI-6024 has shown promising results in clinical trials involving adult and adolescent patients with type 1 diabetes.

Synthesis

NBI-6024 was synthesized by the solid phase methodology in a Beckman model 900 peptide synthesizer using a Merrifield resin. The α-amino function of the peptides was protected with the *tert*-butoxycarbonyl (Boc) group. Side chain functional groups of the amino acids were protected as follows: benzyl for serine, cyclohexyl for glutamic acid and tosyl for histidine and arginine. Coupling of the terminal carboxylic amino acid to the resin was performed with DCC. When the last amino acid was introduced, the terminal Boc group was removed and the resin was cleaved with HF and anisole (1).

Introduction

Diabetes mellitus type 1, also known as juvenile-onset or insulin-dependent diabetes mellitus (IDDM), is characterized by autoimmune destruction of pancreatic beta-cells resulting in the inability of the pancreas to produce insulin. It can be caused by autoimmune, genetic and/or environmental factors and it accounts for 5-10% of all reported cases of diabetes mellitus. Thus, as many as 10-11 million individuals suffer from this form of diabetes worldwide, with approximately 1 million afflicted in North America alone. Type 1 diabetes usually develops before the age of 40 with most cases presenting before the age of 20. Peak incidence occurs at age 5-7 years (2).

The standard therapy currently available for type 1 diabetes is daily insulin injections to control blood glucose levels. However, insulin does not influence natural disease progression nor does it prevent the onset of the disease. In addition, insulin administration is associated with complications and, if administered incorrectly, can cause irreversible and/or life-threatening adverse events. Thus, research has focused on therapies which can both manage and prevent type 1 diabetes onset (2).

In type 1 diabetes, healthy pancreatic beta-cells are mistakenly targeted by the immune system as being foreign. The result is immune-mediated destruction of the pancreatic β-cells responsible for insulin production. Type 1 diabetes is predominantly preconditioned by genetic factors and relatives of individuals suffering from the disease have a significantly increased risk of developing the disease. However, environmental factors may also trigger the disease since a large number of

L.A. Sorbera, J. Castañer, M. Bayés. Prous Science. P.O. Box 540, 08080 Barcelona, Spain.

Table I: Clinical studies of NBI-6024 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Type 1 diabetes mellitus	Randomized, double-blind, multicenter	NBI-6024, 0.1 mg s.c. s.d. (n=4) NBI-6024, 0.5 mg s.c. s.d. (n=4) NBI-6024, 1 mg s.c. s.d. (n=4) NBI-6024, 5 mg s.c. s.d. (n=4) NBI-6024, 10 mg s.c. s.d. (n=4) Placebo (n=5)	20	Subcutaneous NBI-6024 as a single dose up to 10 mg was well tolerated in patients with insulin-dependent diabetes mellitus	3
Type 1 diabetes mellitus	Randomized, double-blind, multicenter	NBI-6024, 0.1 mg s.c. 1x/2wk x 8 wk NBI-6024, 0.5 mg s.c. 1x/2wk x 8 wk NBI-6024, 1 mg s.c. 1x/2wk x 8 wk NBI-6024, 5 mg s.c. 1x/2wk x 8 wk NBI-6024, 5 mg s.c. 1x/2wk -> 1x/1mo Placebo	30	Subcutaneous NBI-6024 as a multiple dose up to 5 mg was well tolerated in patients with insulin-dependent diabetes mellitus	4
Type 1 diabetes mellitus	Randomized	NBI-6024, 0.1 mg 1x/2wk x 8 wk NBI-6024, 1 mg 1x/2wk x 8 wk NBI-6024, 5 mg 1x/2wk x 8 wk Placebo NBI-6024, 1 mg 1x/2wk x 4 wk -> 1x/1 mo x 2 mo NBI-6024, 5 mg 1x/2wk x 4 wk -> 1x/1 mo x 2 mo Placebo	35	NBI-6024 was well tolerated in adolescent patients with insulin-dependent diabetes mellitus	5

new-onset patients do not have relatives with the disease. These environmental factors may initiate the autoimmune destruction of β-cells and, in this regard, diabetes type 1 may be preventable (2).

One novel approach to both preventing and managing type 1 diabetes is the development of diabetes vaccines which downregulate immune-mediated pancreatic β-cell destruction. In addition to NBI-6024, there are currently 2 other such vaccines in phase II development: DiaPep277 (Peptor) and rhGAD65 (Diamyd Medical) (2).

NBI-6024 consists of an altered peptide ligand (APL) which is a dominant pancreatic antigen (*i.e.*, immunodominant T-cell epitope) that was engineered so that it can no longer be recognized by autoreactive immune cells. APL has been shown to downregulate immune-regulated destructive process in nonobese diabetic (NOD) mice resulting in preservation of pancreatic β-cells and insulin production and, thus, the prevention of hyperglycemia. In addition, APL has been shown to reduce the incidence of diabetes in preclinical models, indicating that the agent has the potential to intervene in the onset of type 1 diabetes especially in those individuals who are at a high risk for the disease and in newly diagnosed patients or patients who still have residual intact β-cell function. NBI-6024 has been selected for further clinical development for the prevention and treatment of type 1 diabetes (2).

Clinical Studies

The safety and tolerability of single-dose NBI-6024 (0.1, 0.5, 1, 5 and 10 mg s.c.) were demonstrated in a multicenter, randomized, double-blind, placebo-controlled, dose-escalation study involving 20 nonsmoking, healthy male adults (18-50 years) suffering from type 1 diabetes (HbA1c < 9%). Injections of the agent were administered during a 36-h in-clinic stay and patients were followed for up to 3 months posttreatment. Glucose control, incidence of adverse events, vital signs, ECG and physical exams and laboratory parameters obtained from NBI-6024-treated patients were similar to those obtained from placebo-treated patients. No serious adverse events were observed and no patients discontinued or withdrew (3). The results of this study and the following 2 studies are summarized in Table I.

Multiple-dose NBI-6024 (0.1, 0.5, 1 and 5 mg s.c. biweekly for a total of 5 doses over 8 weeks or 5 mg biweekly followed by monthly) was also shown to be safe and tolerable in a multicenter, randomized, placebo-controlled, double-blind, sequential dose-escalation study involving 30 healthy males (18-50 years) with type 1 diabetes (HbA1c < 10%) who were followed for up to 12 months after the first dose. The agent was well tolerated. Two serious adverse events of hypoglycemia were reported although they were concluded not to be associated with NBI-6024. The most common adverse event was burning at injection site. Incidence of adverse events, physical exam, vital signs, ECG, glucose control and laboratory parameters were similar for both NBI-6024- and placebo-treated groups (4).

Results from a phase I/II multicenter, randomized, double-blind, placebo-controlled, sequential dose-escalation study involving 35 adolescents (12-17 years) with type 1 diabetes reported that multiple-dose NBI-6024 (0.1, 1 or 5 mg s.c. biweekly for a total of 5 doses over 8 weeks or 1 or 5 mg biweekly for 4 weeks followed monthly for 2 months for a total of 5 doses over a 12-week

period) was safe and well tolerated. All adverse events seen during the study were concluded to be unrelated to NBI-6024. The most common adverse events were upper respiratory infection and headache. Three serious adverse events not attributed to NBI-6024 were observed in 3 patients and included gastritis, vomiting and hypoglycemic coma with seizure due to insulin overdose. Similar safety profiles including physical exams, vital signs, laboratory parameters, Tanner staging and injection site assessments were obtained for NBI-6024 and placebo groups (5).

NBI-6024 is currently undergoing 2 pivotal phase IIb, multicenter, randomized, double-blind, placebo-controlled, multiple-dose, dose-ranging trials involving approximately 600 adult and adolescent patients with new-onset type 1 diabetes. The trials are examining the safety, tolerability and efficacy of 3 doses of NBI-6024 administered s.c. for at least 1 year as compared to placebo. The primary endpoint of the trials is the effect of multiple-dose NBI-6024 in preserving endogenous insulin secretion as measured by C-peptide levels and in delaying disease progression (6, 7).

Source

Neurocrine Biosciences Inc. (US); licensed to Taisho Pharmaceutical Co., Ltd. (JP).

References

1. Gaur, A., Ling, N., Conlon, P.J. (Neurocrine Biosciences Inc.). *Methods for treatment of diabetes using peptide analogues of insulin.* US 6197926, WO 9942482.

2. Prous Science Drug R&D Backgrounders: *Diabetes mellitus (online publication).* Updated September 4, 2002.

3. Scholtz, H., Jochelson, P., Allen, D.M., Patel, S.S., Conlon, P., Campbell, B. *Single dose safety and tolerability of NBI-6024: A new altered peptide ligand for type 1 diabetes mellitus.* Diabetes 2001, 50(Suppl. 2): Abst 522-P.

4. Distiller, L.A., Bonnici, F., Areti, P., Scholtz, H.E., Allen, D.M., Jochelson, P. *Multiple-dose safety and tolerability of NBI-6024: A new altered peptide ligand for type 1 diabetes mellitus.* Diabetes 2001, 50(Suppl. 2): Abst 1808-PO.

5. Philotheou, A., Distiller, L., Bonnici, F., Mollentze, W.F., Ashinger, A., Jimenez, R., Tomlin, R., Jochelson, P. *A randomized, double-blind, placebo-controlled, multi-center, sequential, dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of multiple doses of NBI-6024 in adolescent patients with insulin dependent type 1 diabetes mellitus.* Diabetes 2002, 51(Suppl. 2): Abst 453-P.

6. *Phase I/II program for NBI-6024 expanded; pivotal phase IIb trial to commence later this year.* DailyDrugNews.com (Daily Essentials) February 23, 2001.

7. *Phase IIb clinical trial of NBI-6024 in diabetes set to commence.* DailyDrugNews.com (Daily Essentials). January 4, 2002.