

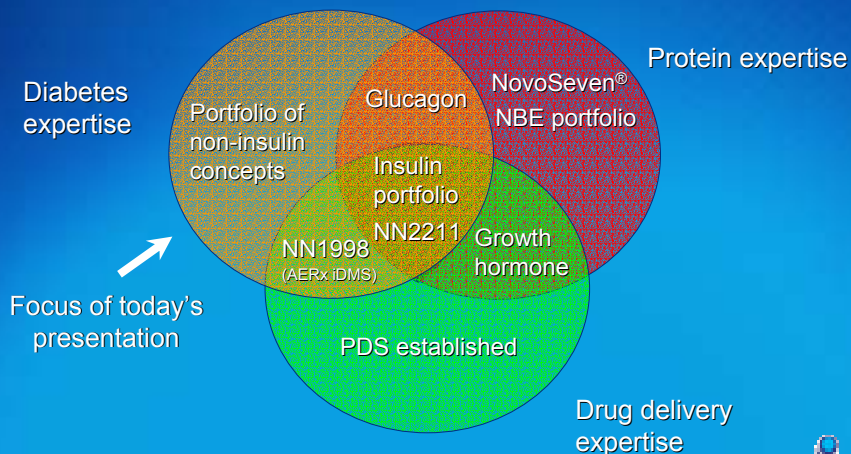
# Novo Nordisk

*A focused global healthcare company*

Treatment of diabetes  
Presentation at Alfred Berg  
11 October 2002



## Novo Nordisk's R&D core competencies

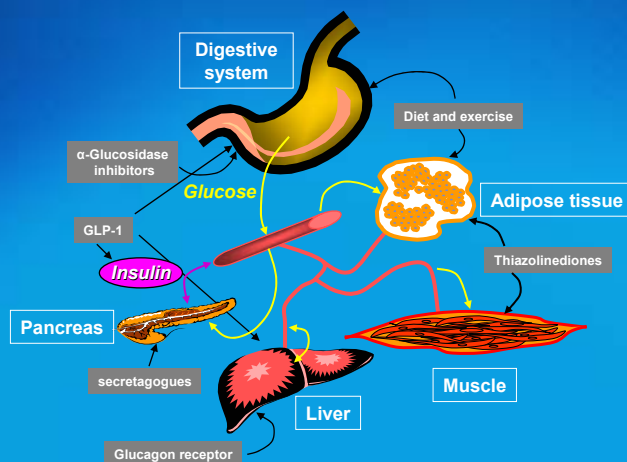


# Agenda

- Diabetes - Novo Nordisk's approach to the metabolic syndrome
- Late state development projects
  - NN2211
  - NN1998 (AERx iDMS)
  - NN304 (detemir)
- Research – key for future development
- Highlights from EASD - the post prandial regulation

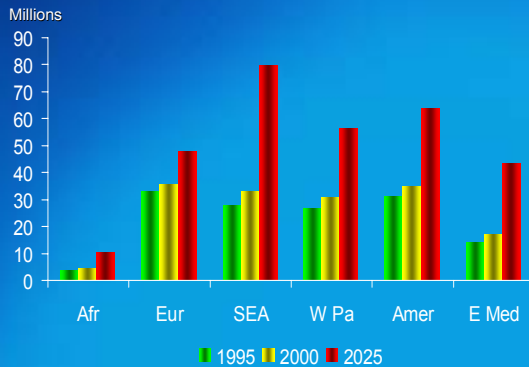


# The metabolic syndrome

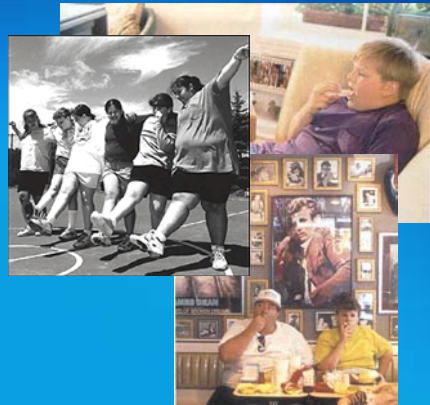


# An unfolding epidemic

Estimated number of people with diabetes

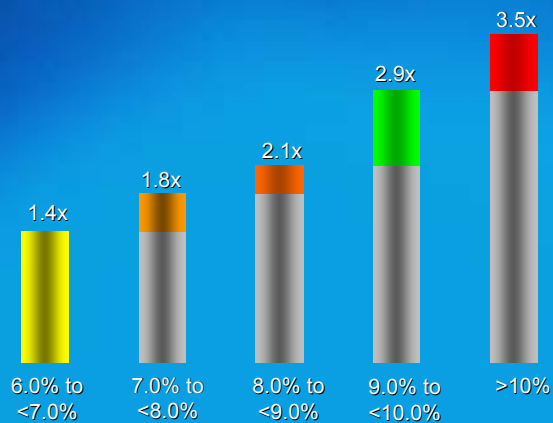


Source: WHO, 1997



# Poor control leads to higher risk

Risk of any complication relative to HbA1c below 6.0%

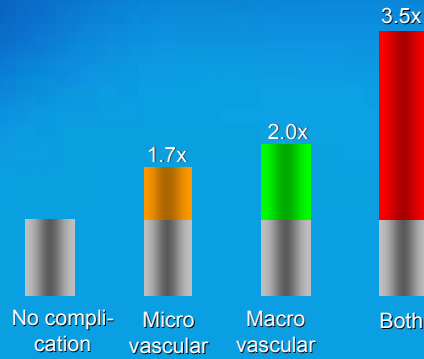


Source: Adapted from UKPDS 35



# Late stage complications a huge burden

Relative cost of diabetes complications

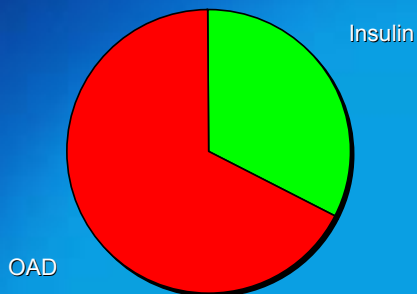


Note: Cost for society relative to no complication  
Source: Adapted from Rhys Williams, IDF



# Today's treatment - a USD 11 bn market

Split of treatment of diabetes

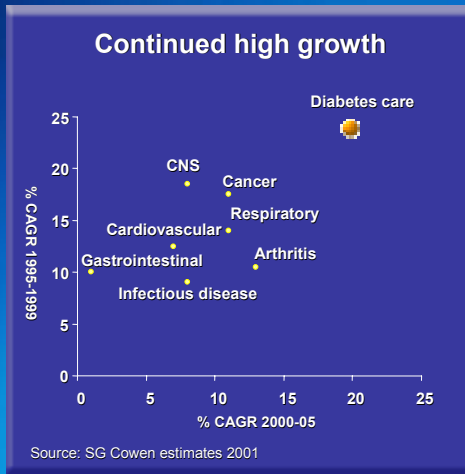


Selected market dynamics:

- Market growing at 15% MATQ2 2002
- Insulin market:
  - Stable volume growth
  - Value upgrade adding to growth
- OAD market:
  - Slow down of growth due to Glucophage of patent
  - Growth primarily driven by volume



# A high growth therapeutic area

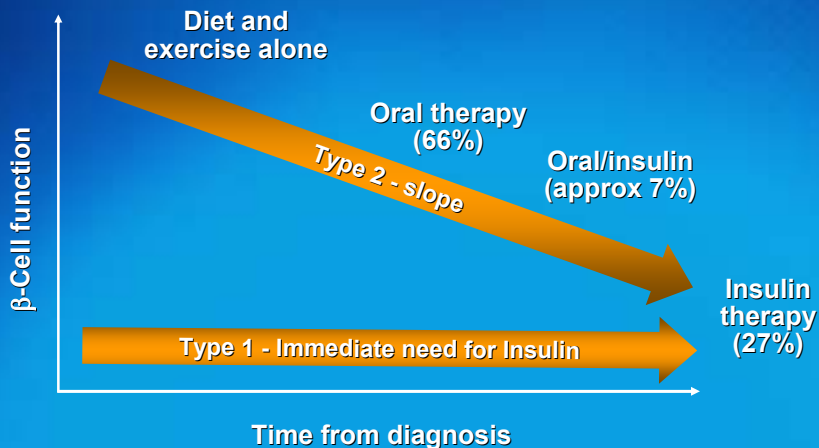


Key Novo Nordisk features:

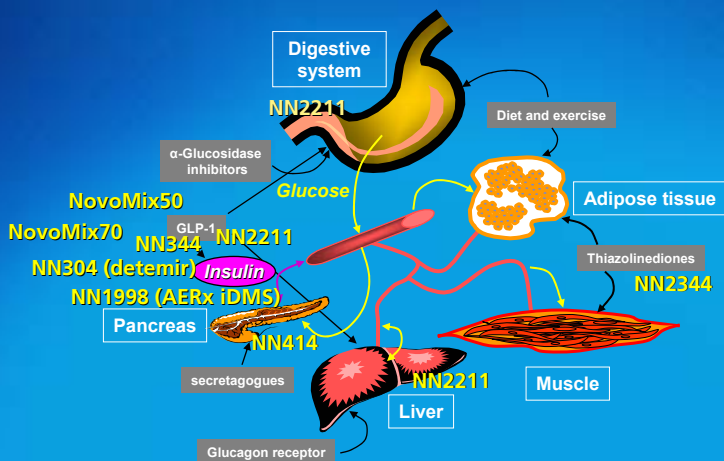
- Leading company in diabetes treatment
- Leadership in insulin
  - #1 in Europe and Japan
  - #2 in USA
- Broadest analogue portfolio
- Broadest device portfolio
- Most comprehensive Type 2 diabetes pipeline in the industry



# Insulin – the ultimate diabetes therapy



# The Novo Nordisk approach in development



# Diabetes care development pipeline

## Phase 1

- NN414 (Beta cell rest)
- NN344 (Basal insulin analogue)

## Phase 2

- NN2344 (Insulin sensitiser)
- NN2211 (GLP-1 analogue)

## Phase 3

- NN304 (Insulin detemir)
- NN1998 (AERx@IDMS)
- NovoMix® 50 (Premixed analogue)
- NovoMix® 70 (Premixed analogue)

Note: Clinical development of ragaglitazar (NN622) was suspended in July 2002.

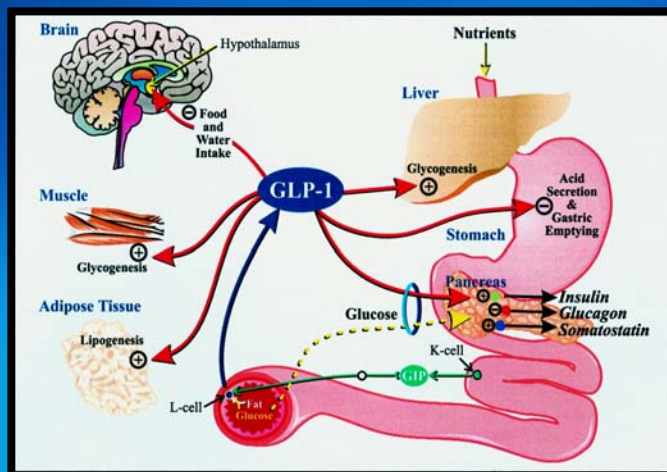


# NN2211 – GLP-1 analogue

The first and only once daily human GLP-1 derivative for the treatment of type 2 diabetes



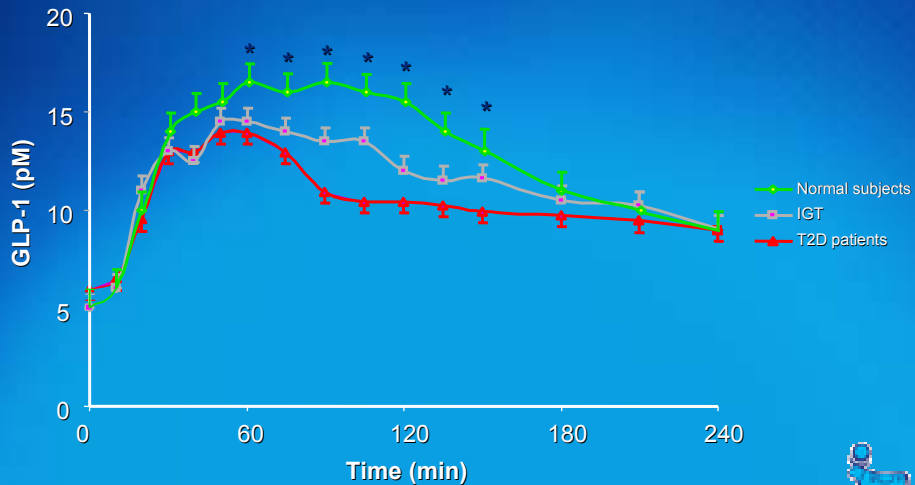
## Native GLP-1 is an intestinal hormone



Kieffer & Habener (1999): Endocrine Reviews 20: 876-913



## Type 2 diabetics have impaired GLP-1 secretion

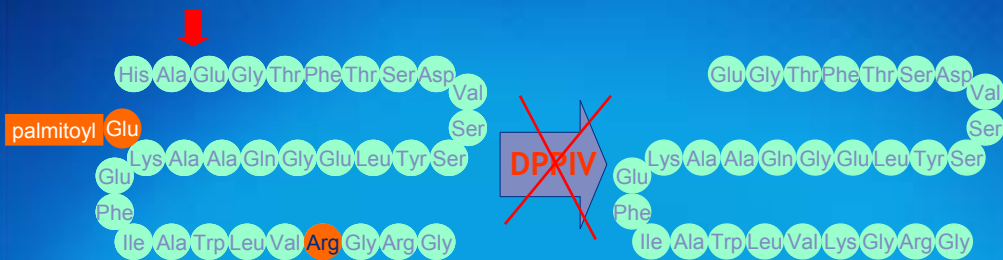


Adapted from Toff-Nielsen et al. ( 2001): J Clin Endocrinol Metab 86:3717-3723



## GLP-1 is rapidly degraded by DPPIV

NN2211



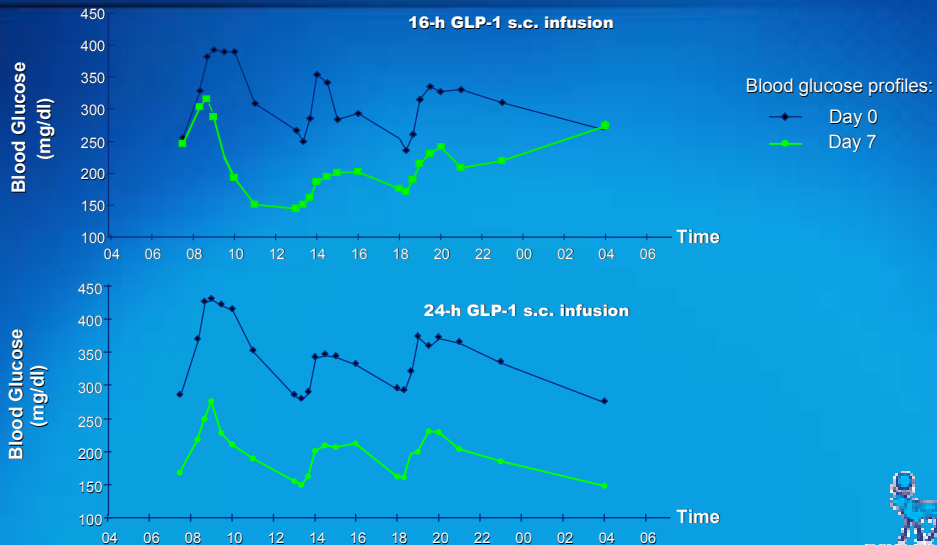
- Acylation of GLP-1 leads to **ACTIVE** GLP-1 (1-37)
- Resistance to DPPIV
  - Reduced renal elimination
  - Once daily dosing

GLP-1 (9-37)  
**INACTIVE**



## Human GLP-1 has a very short half-life:

24 hours coverage is needed for optimal effect



Source: Modified from J Larsen et al: Diabetes Care 2001; 24:1416-1421



## Two concepts in current development

### Human GLP-1 based derivatives/analogues

- NN2211 (Novo Nordisk)
- LY307161 (Eli Lilly) – discontinued
- Others

### Gila monster Exendin-4 based (Approx 50% different from human GLP-1)

- Exendin-4/AC2993 (Amylin/Eli Lilly)
- ZP-10 (Zealand Pharmaceuticals)
- Others



# Key issues regarding the two concepts

## Human GLP-1 based

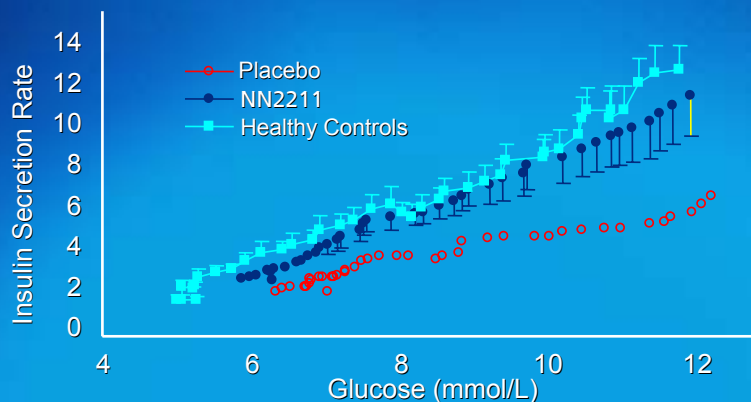
- Once daily injection
- Peakless
- Low incidence of nausea (NN2211 only)
- No immunogenicity issue
- Injection site reaction not GLP-1 effect but formulation specific (LY307161 SR only)

## Exendin based

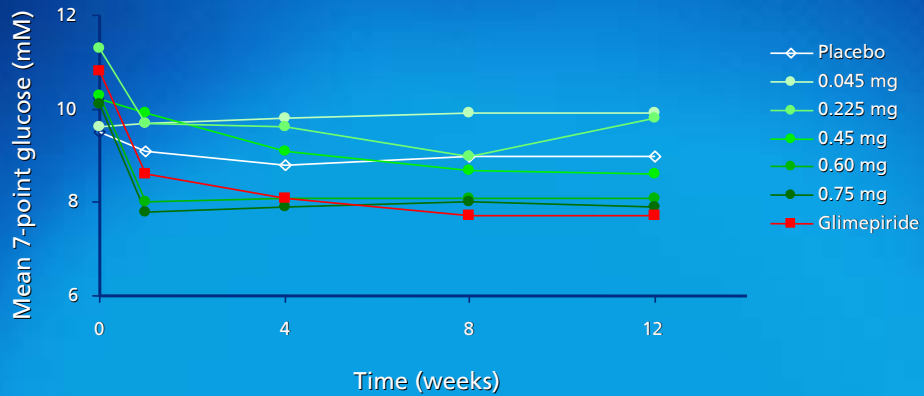
- Twice daily injection
- Distinct peak
- Higher incidence of nausea
- Immunogenicity issue
- Attempts at prolonging action may lead to injection site reactions



## Single-dose NN2211 normalise beta cell sensitivity to glucose in type 2 diabetes



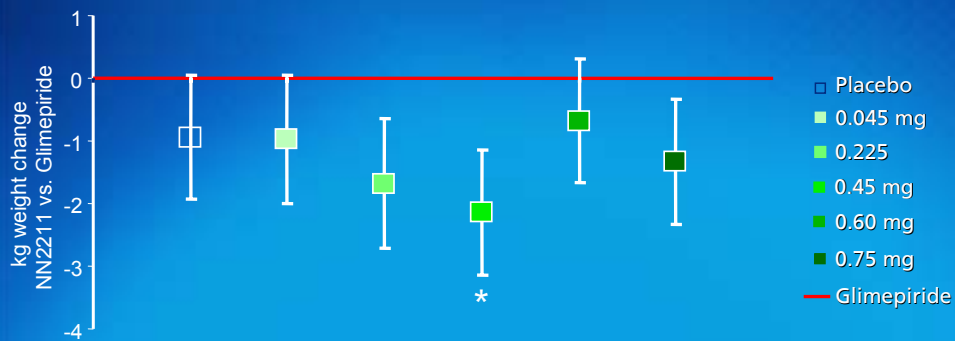
# Full glycaemic control within 1 week



Matthews et al. 2002: ADA 2002



# NN2211 controls weight compared to SU



Note: Mean values with 95%CI; \* = P < 0.05  
Source: Matthews et al. 2002: ADA 2002



## NN2211 - The first once daily human GLP-1 derivative

Key observations from studies so far:

- No or low hypoglycaemic risk
- Glycaemic control sustained over 3 months
- Maximum effect on blood glucose in 1 week
- Weight control
- One daily injection
- $\beta$ -cell mass increase in animal models



## NN304 – detemir

The predictable basal insulin



# Evolution of long-acting insulins at Novo Nordisk

<u>Animal insulin</u>	<u>Human insulin</u>	<u>Insulin analogue</u>
<b>1938:</b> Nordisk patented protamin zinc insulin	<b>1952:</b> Novo marketed "Lente"	<b>1982:</b> Both Lente and NPH is introduced as human insulin
<b>1946:</b> Nordisk issued patents on neutral protamin Hagedorn (NPH)	<b>1970:</b> Novo introduced MC insulins	<b>2002E:</b> NN304 to be filed at the turn of the year



## Selected short-comings of long-acting human insulin

### Key observations:

- The distinct peak of action after 5-7 hours of NPH cause
  - frequent hypoglycaemia during the night
  - high blood glucose in the morning
- Most "long-acting" products are too short-acting
- Large variation in day-to-day action
- Weight gain
- Risk of tissue reaction
- Must be mixed thoroughly before injection



# Strategies for engineering a long-acting insulin analogue

## Strategies:

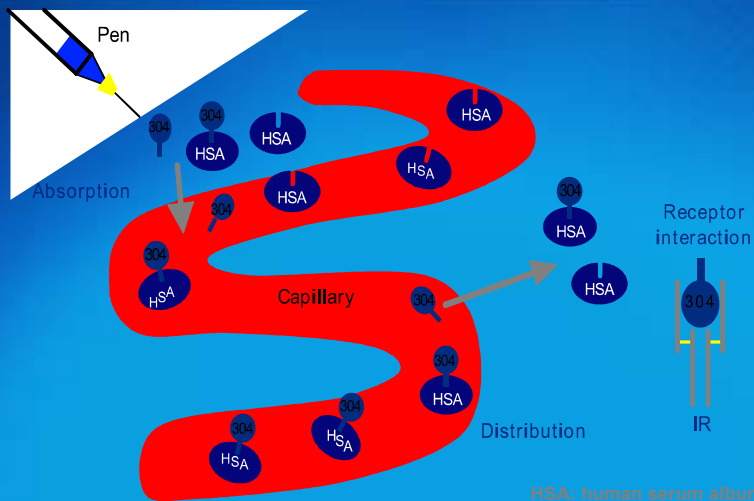
- Modify isoelectric point to provide precipitation at pH 7.4
  - NovoSol Basal (A21Gly,B27Arg,B30ThrNH2)
  - Insulin glargine (Lantus) (A21Gly, B31B32diArg)
- Strengthen hexamer-association
  - Co(III)-hexamer
- Acylation with hydrophobic residues
  - Insulin detemir (NN304) (B29Lys(myristoyl), des(B30))

## Comments:

- The products are long-acting with rather flat profiles, but with this concept, the action profile is still very variable from day to day
- These products were long-acting, but caused unacceptable reactions at the injection site
- This concept provides products with flat profiles and very low variability



# NN304 (detemir) – mechanism of protraction



## NN304 (detemir) properties

- Soluble at neutral pH:
  - No re-suspension required
  - Low risk of injection pain
- Physiologic profile
  - Flatter, smoother action profile than NPH
- Flexible
  - Once- or twice daily dosing according to patient needs
- Low intra-patient variability:
  - Predictable action profile
  - Low risk of hypoglycaemia
- Short term safety:
  - Reduced risk of hypoglycaemia compared to NPH
- Long term safety
  - Low IGF-1 receptor affinity
  - Low mitogenic risk
  - Reduced hypoglycaemia
  - No weight gain



## NN1998 (AERx iDMS)

Earlier treatment with insulin



# Pulmonary delivery – the next step



- Historical standard

1921



- Patient friendly
- Single unit increments
- Precision dosing

1980s

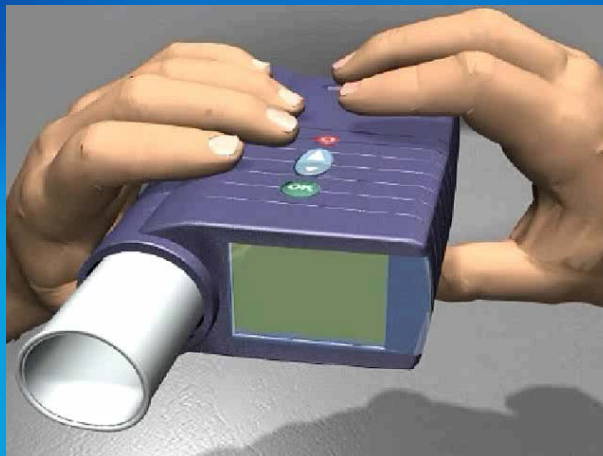


- Patient friendly
- Single unit increments
- Precision dosing
- Needle free

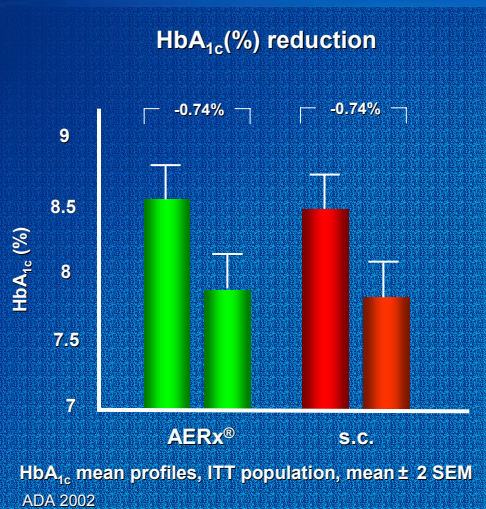
>2005



# NN1998 (AERx) – How it works



# Our inhaled insulin – as effective as injected



## Key observations from Phase 2:

- Deep lung deposition of aerosols
- “Breath Check”, one unit increments, highly reproducible delivery
- Rapid-acting profile, one unit increments and patient-friendly features
- Glycemic control equal to that of intensive treatment with s.c. human insulin
- Lower tendency of hypoglycemic events
- No major safety or technical issues



## NN1998 (AERx iDMS): Pros and cons

	AERx® iDMS	Exubera™
<ul style="list-style-type: none"> <li>Dosing (per load)</li> </ul>	Insulin strip (partial dosing from 2 to 10 UNITS) liquid	Insulin blister (3 UNIT or 9 UNIT blister) powder
<ul style="list-style-type: none"> <li>Dosing (eq. Units)</li> </ul>	1 UNIT	3 UNITS
<ul style="list-style-type: none"> <li>Dosing regime</li> </ul>	“UNITS”	“MG”
<ul style="list-style-type: none"> <li>Breathing pattern</li> </ul>	Controlled by “Breath Check”	No control
<ul style="list-style-type: none"> <li>Mealtime delivery</li> </ul>	YES	YES
<ul style="list-style-type: none"> <li>Compliance monitoring</li> </ul>	YES	NO
<ul style="list-style-type: none"> <li>Absorption enhancers</li> </ul>	NO	NO

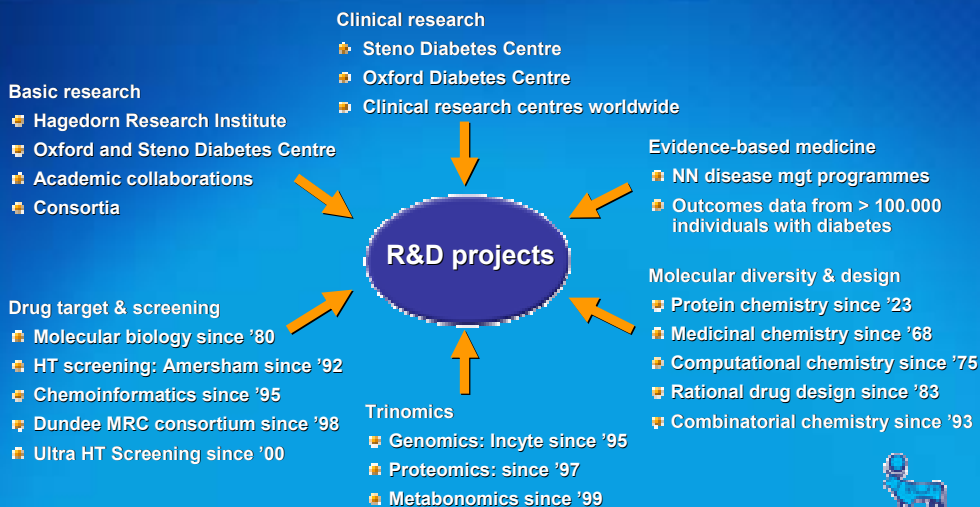


# Research

## Key to future development

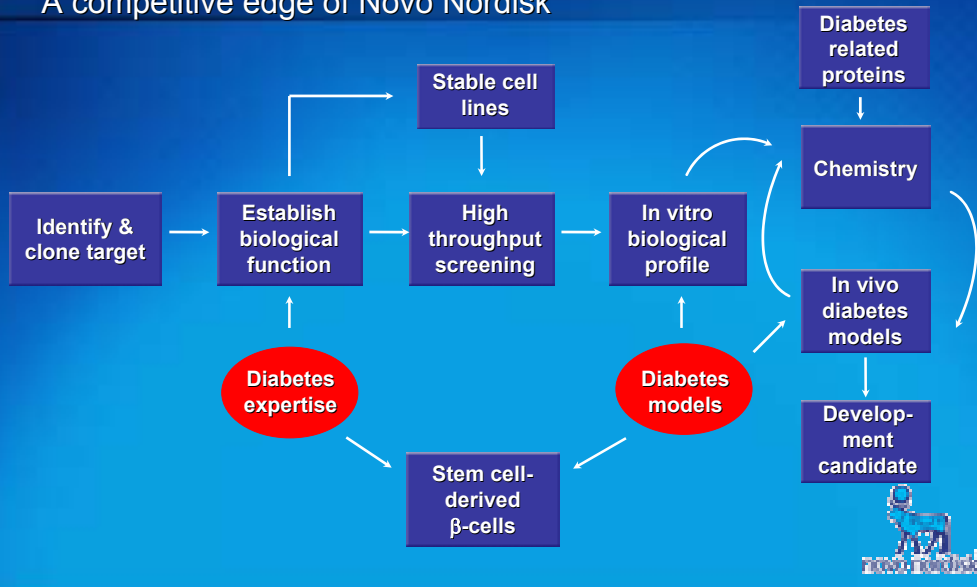


# Diabetes – Sources of Innovation at Novo Nordisk



# Evolution of a Diabetes Project:

A competitive edge of Novo Nordisk



## EASD - highlights

### Key observations at EASD 2002

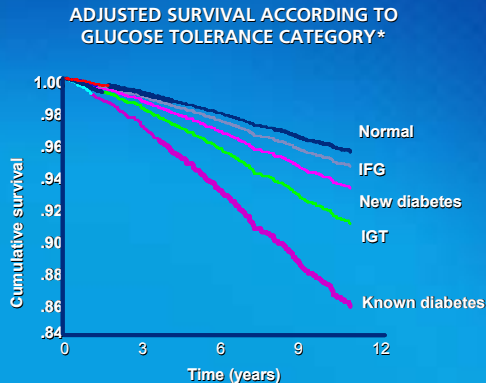
- Much attention paid to optimizing insulin therapy regimens
- Insulin delivery systems (injection, inhalation, CSII etc) in focus
- Strong scientific interest in GLP-1 and its role in type 2 diabetes
- Surprisingly little news on insulin sensitisers
- Negative data, again, from major diabetes prevention trial (ENDIT)



# EASD and the post prandial concept

Why post prandial regulation?:

- The ideal treatment of type 2 diabetes is to mimic the physiological insulin secretion response
- Post-prandial hyperglycaemia (IGT) is strongly associated with cardiovascular morbidity and mortality



\* Cox proportional hazards all cause mortality adjusted for age & ethnicity in 4253 men from Mauritius, Nauru & Samoa



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## Share information

Novo Nordisk's B shares are listed on the stock exchanges in Copenhagen and London. Its ADSs are listed on the New York Stock Exchange under the symbol "NVO". For further company information, visit Novo Nordisk on the World Wide Web at

<http://www.novonordisk.com>

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