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# The Non-inferiority Margin in Diabetes Trials

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# Outline

- What is diabetes?
- Measuring efficacy in diabetes trials
- Regulatory guidance on non-inferiority
- Balancing deficits against benefits
- Price negotiations
- Summary and discussion

# Disclaimer

- The views expressed in this talk represents that of those speaker and not necessarily Novo Nordisk

# What is diabetes mellitus?

- Diabetes is a disease characterised by persistent hyperglycaemia
  - hyperglycaemia = elevated blood glucose conc.
- Persistent hyperglycaemic is caused by insufficient availability of insulin as a result of
  - failure in the endocrine system
    - insufficient insulin secretion
    - type 1 diabetes (juvenile diabetes)
  - insulin resistance
    - tissue insensitive to insulin
    - type 2 diabetes (senile diabetes)

# Long term complications to diabetes

- Persistent hyperglycaemia increase the risk of
  - microvascular complications
    - retinopathy (eye disorder)
    - nephropathy (kidney disorder)
    - neuropathy (nerve disorder)
  - macrovascular complications
    - arteriosclerosis (thickening of arterial walls)
    - increased tendency to infections

# Glycosylated Hemoglobin A1c (HbA1c)

- Persistent hyperglycaemia can be assessed by HbA1c
  - HbA1c percentage of hemoglobin that is glycosylated
    - Hemoglobin carries oxygen from the lungs to the rest of the body and carbon dioxide back
    - Glucose stick to hemoglobin
- HbA1c correlates well with average blood glucose over a 3-months period
  - Nathan et al. (2008)
- The target for treatment of diabetes is  $\text{HbA1c} \leq 7\%$ 
  - ADA target

# Measuring persistent hyperglycaemia

- In both clinical practice and controlled trials HbA1c is the most important biomarker for assessing long term hyperglycaemia
- Standardised assays exist for measuring HbA1c
  - NGSP and IFCC assays
- HbA1c is used uniformly across diabetes trials as the primary efficacy endpoint

# Showing differences in HbA1c

- Insulin is often used in the treatment of diabetes, since insulin is the most efficient drug in lowering blood glucose
- In trials comparing one insulin preparation to another it can be difficult to show differences in HbA1c
  - all insulin preparations are individually titrated
  - dose titration using a pre-specified algorithm is often used in insulin trials to ensure appropriate treatment of subjects
- For these reasons trials comparing different insulin preparations are almost exclusively designed as non-inferiority trials



## Example: The NOVEL-1 trial

- NOVEL-1 is a randomised, controlled, 1-year, multinational, parallel-group trial investigating efficacy and safety of insulin detemir in subject with type 1 diabetes
- 447 subjects randomised 2:1 to
  - insulin detemir
  - insulin glargine

## Results for HbA1c (%)

	Detemir	Glargine
#subjects	283	134
Baseline mean (SD)	8.1 (1.1)	8.2 (1.2)
Change from Baseline mean (SD)	-0.53 (0.84)	-0.54 (0.69)

	ITT analysis	PP analysis
Detemir – Glargine	0.01 [-0.13, 0.16]	-0.01 [-0.16, 0.15]

# Declaring Non-inferiority

- Is it possible to claim non-inferiority of Detemir versus Glargine based on these results?
- From a practical point of view we could say that
  - there's hardly any difference between the HbA1c reductions
  - ITT and PP comes out on opposite sides of zero
  - so if the trial is not too small we should suspect that the two products (or regimens) have similar HbA1c lowering potential
- From a statistical point of view we know that
  - it solely depends on the non-inferiority margin
    - but how to select the non-inferiority margin?

# Regulatory guidance

- ICH-E9 (1998)
  - Statistical principles for clinical trials
- ICH-E10 (2001)
  - Choice of control group and related issues
- EMEA (2007)
  - Guideline on the choice of non-inferiority margin
- EMEA (2002)
  - Guidance on clinical investigation of medicinal products in the treatment of diabetes mellitus
- FDA (2008)
  - Diabetes mellitus: developing drugs and therapeutic biologics for treatment and prevention

## EMA guidance (2002)

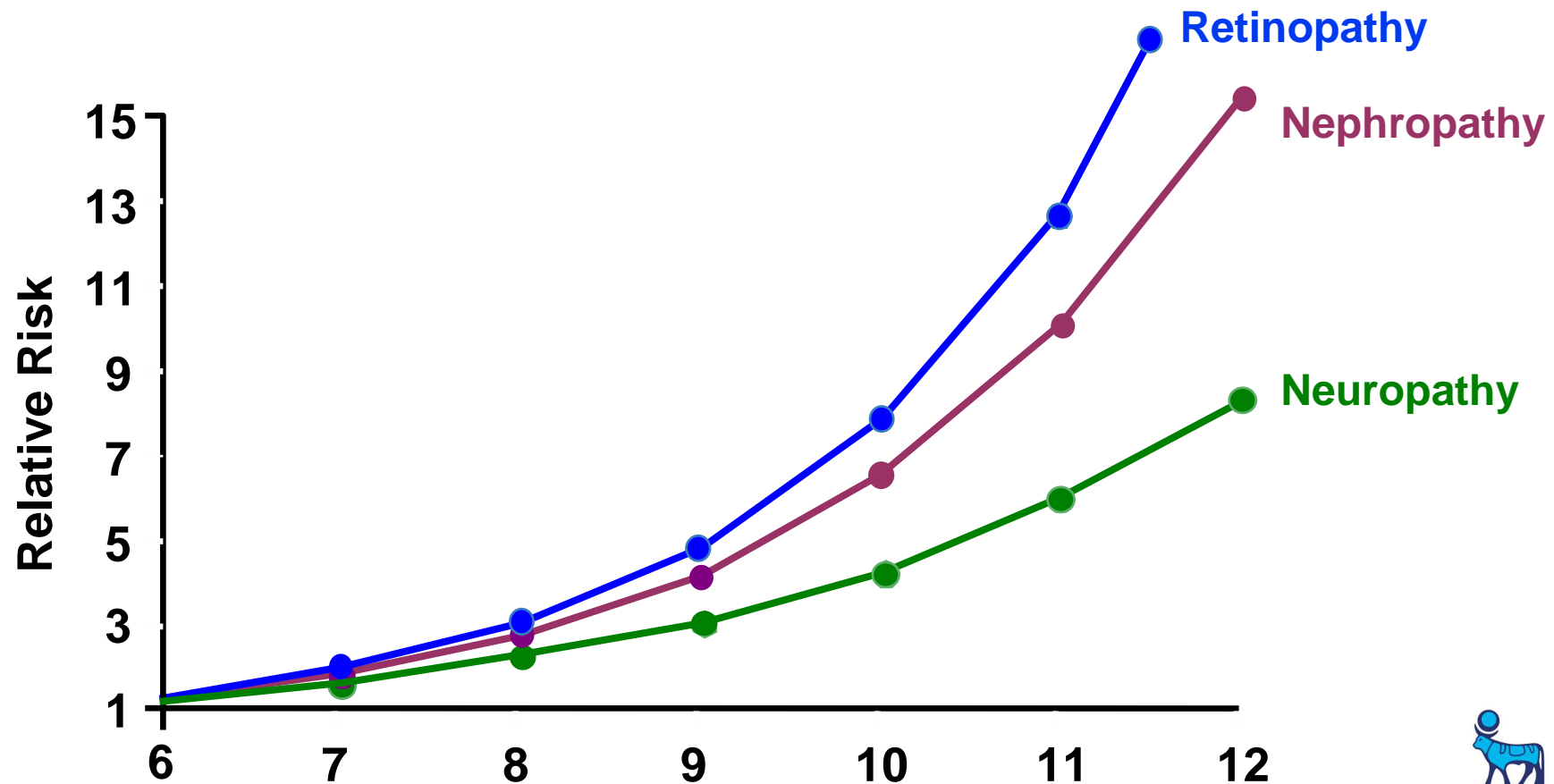
- “an even apparent small difference in HbA1c is considered clinically relevant in terms of risk reduction of diabetic complications”
- “necessary to balance the degree of potential non-inferiority against some other clinical advantage”
- “applicant should demonstrate that this advantage can be equated to the loss of efficacy in some sense”
  - page 6

# HbA1c deficit versus other benefits

- How to equate loss of efficacy to other clinical advantages?
- What is a given HbA1c deficit equal to in terms of for instance increased risk of microvascular complications?
  - depends on the type of complication
  - depends on the baseline HbA1c value
    - cf. the next slide

# Microvascular Complications and HbA1c values

- The risk of microvascular complication increases non-linearly with increasing HbA1c
  - cf. results from DCCT



## HbA1c and risk reduction

- So if a new drug lowers HbA1c more than a standard drug for subjects with high baseline HbA1c, but less for subjects with low baseline HbA1c, it could be that
  - the new drug is inferior to the standard drug in terms of lowering HbA1c on average
  - the new drug is superior to the standard drug in terms of lowering microvascular risk on average
- In such cases the new drug has a clear clinical advantage even if the HbA1c lowering effect is inferior on average



# Balancing against other benefits

- Even without a treatment times baseline interaction other benefits of the new drug may outweigh a possible HbA1c deficit
- Need to balance a deficit in HbA1c lowering effect against other benefits of the new drug in terms of e.g.
  - fewer hypoglycaemic episodes
  - fewer injection site reactions
  - less weight gain
  - improved convenience of administration
  - improved compliance
  - improved lipid profile
  - improved cardiovascular profile
  - etc.

# Health Care Balance

- Balancing a deficit in HbA1c against potential benefits of a product could be done in a health care evaluation in terms of
  - cost to health care system
  - cost to the society in general
  - quality of life
  - life expectancy
  - etc.

# Consistency and Transparency

- The outcome of such health economic evaluations would presumably differ from
  - country to country
  - company to company
  - drug to drug
  - trial to trial
- This would lead to loss of simplicity, consistency and transparency in the non-inferiority concept when balancing a HbA1c deficit against other benefits
- Better to have regulatory authorities dictating a non-inferiority margin common to all anti-diabetic drugs, companies and countries

# The non-inferiority margin

- Recently the FDA issued a draft guidance on diabetes trials, in which a non-inferiority margin was provided
- “Typically, we accept a non-inferiority margin of 0.3 or 0.4 HbA1c percentage units provided this is no greater than a suitably conservative estimate of the magnitude of the treatment effect of the active control in previous placebo-controlled trials.”
  - FDA (2008) page 27

# Placebo-controlled insulin trials

- Placebo-controlled trials usually not possible with insulin
  - placebo-insulin is unethical for all trials in type 1 diabetes
    - survival for type 1 diabetics depends on daily injections of insulin
  - placebo-insulin is considered unethical for most trials in type 2 diabetes
    - placebo insulin would be up-titrated to huge doses and hence volumes to inject
    - type 2 is a progressive disease

# Placebo effect in diabetes

- Type 1 diabetes:
  - insulin treatment effect is typically around 0.5%-1%
    - if type 1 diabetics had their insulin substituted with placebo, the HbA1c would continue to increase until diabetic coma and later death occurred
  - hence the insulin treatment effect versus placebo in type 1 diabetes is larger than 0.5%, which again is larger than the required 0.4%
- Type 2 diabetes:
  - insulin treatment effect is typically around 1%-2%
    - the HbA1c reduction with placebo non-insulin anti-diabetics is typically in the interval from -0.5% to +0.5%
  - hence the insulin treatment effect versus placebo in type 2 diabetes is larger than 0.5%, which again is larger than 0.4%

# Balancing deficits against benefits on price

- With 0.4% as a universally accepted non-inferiority margin the simplicity, transparency and consistency of the non-inferiority concept is maintained across trials, countries and products
- The balance of HbA1c deficit against other benefits will automatically come into play in the price negotiations in the different countries, where the product is to be launched
- The price of a product will by default differ from
  - country to country
    - depending on the reimbursement and health care system
  - drug to drug
    - depending on the deficit-benefit balance

# Self-regulation through the price

- So the market price of a product would prevent slightly inferior (though statistically non-inferior) products without any other benefits to reach the market
  - if a drug is non-inferior but has less efficacy and no real benefits to balance this deficit
    - market price of the drug would very low
    - business case for the drug would be unattractive
    - drug will not be marketed



# Summary and discussion

- The primary efficacy endpoint in diabetes trials is HbA1c
  - despite the many advantages of HbA1c, it does not provide all relevant information
    - other benefits may outweigh a deficit in HbA1c lowering effect
  - in balancing benefits against deficits the non-inferiority concept loses its simplicity, transparency and consistency
- To maintain simplicity the non-inferiority margin should be dictated by regulatory authorities
  - the price issues will ensure that drug marginally inferior in terms of HbA1c will have other benefits that outweigh the HbA1c deficit



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