

# Liraglutide Treatment of Type 2 Diabetes

FDA Advisory Committee Presentation

April 2, 2009

# Introduction

Mary Ann McElligott, PhD

Associate Vice President, Regulatory Affairs  
Novo Nordisk

# Liraglutide – Important Effects for Diabetes Treatment

- Analogue of human native peptide GLP-1
- Significant improvements in glycemic control
- Clinically relevant secondary endpoints evaluated including weight
- Well tolerated
  - Gastrointestinal side effects most common
  - Low risk of hypoglycemia

# Indication and Dosing for Type 2 Diabetes

- Indication
  - Adjunct to diet and exercise
  - Improvement of glycemic control in Type 2 diabetes
  - Mono- and combination therapy
- Prolonged half-life with once daily dose
  - Independent of meals and time of day
- Daily dosing
  - 0.6 mg/day for one week increased to 1.2 mg
  - Increased to 1.8 mg, as required

# Agenda

## Introduction

**Mary Ann McElligott, PhD**  
Associate Vice President, Novo Nordisk

## Rationale for Developing New Drugs for Type 2 Diabetes

**John B. Buse, MD, PhD**  
Chief, Division of Endocrinology, UNC  
Past-President, Medicine & Science,  
American Diabetes Association

## GLP-1 Pharmacology

**Alan Moses, MD**  
Global Chief Medical Officer, Novo Nordisk

## Efficacy & Safety

**Milan Zdravkovic, MD, PhD, MSc, Pharm Med**  
Corporate Vice President, GLP-1 Development,  
Novo Nordisk

## Clinical Perspectives on Thyroid and Calcitonin

**Gilbert Daniels, MD**  
Co-Director, Thyroid Clinic,  
Massachusetts General Hospital  
Professor of Medicine, Harvard Medical School

## Benefit/Risk Risk Management Plan

**Alan Moses, MD**

# External Experts

- |                      |  |
|----------------------|--|
| Steven Marso, MD     | Clinical Scholar, Mid-America Heart Institute<br>St. Luke's Hospital System<br>Associate Professor of Medicine<br>University of Missouri-Kansas City |
| Jeremy Ruskin, MD    | Director, Cardiac Arrhythmia Service<br>Massachusetts General Hospital<br>Associate Professor of Medicine<br>Harvard Medical School                  |
| Philip S. Schein, MD | Visiting Professor in Cancer Pharmacology<br>University of Oxford  |

# External Experts

Gilbert Daniels, MD

Co-Director, Thyroid Clinic  
Massachusetts General Hospital  
Professor of Medicine  
Harvard Medical School

James Swenberg, DVM, PhD

Kenan Distinguished Professor of  
Environmental Sciences and Engineering  
Director of Toxicology  
Professor of Pathology  
University of North Carolina at Chapel Hill

William Steinberg, MD

Gastroenterologist  
Rockville Internal Medicine Group  
Clinical Professor of Medicine  
George Washington University Medical Center

# Liraglutide Profile

- High glycemic efficacy
- Favorable safety profile
- Responsible Risk Management Program

# Rationale for Developing New Drugs for Type 2 Diabetes

John B. Buse, MD, PhD

Chief, Division of Endocrinology

Executive Associate Dean, Clinical Research

University of North Carolina School of Medicine

# Type 2 Diabetes Epidemic

- Lifetime risk is approximately 1 in 3
- 7.5% of the US population – 23 million people
- More than 1.5 million new cases per year
- Devastating impact on patients through complications
  - Death, amputations, dialysis, blindness
- More effective therapies needed because too few patients achieve target levels of control

# ADA/EASD Consensus Treatment Algorithm Criteria

- Glucose lowering effectiveness
- Non-glycemic effects
  - CVD risk factors
  - Body mass
  - Insulin resistance or insulin secretory capacity
- Safety
- Tolerability, ease of use, expense
- GLP-1 agonists added as a second tier treatment option in combination with metformin

# Why Add GLP-1 Agonist Therapy to the Treatment Algorithm

- Current therapies have some limitations
  - Metformin – GI intolerance and inability to use in renal insufficiency
  - Sulfonylureas – hypoglycemia and weight gain
  - Insulin – hypoglycemia and resistance by patients and physicians
  - Thiazolidinediones – weight gain, bone fractures, fluid retention including congestive heart failure
- GLP-1 receptor agonists have potential to improve diabetes treatment based on
  - Glycemic efficacy
  - Extraglycemic effects (weight, blood pressure, insulin sensitivity and beta-cell function)

# Conclusion

- Diabetes is a serious problem in the US
- Most patients do not achieve adequate control of diabetes and its comorbidities due in part to:
  - Inadequate therapies
  - Complicated treatment regimens
- GLP-1 agonists offer great promise for diabetes treatment

# GLP-1 Pharmacology

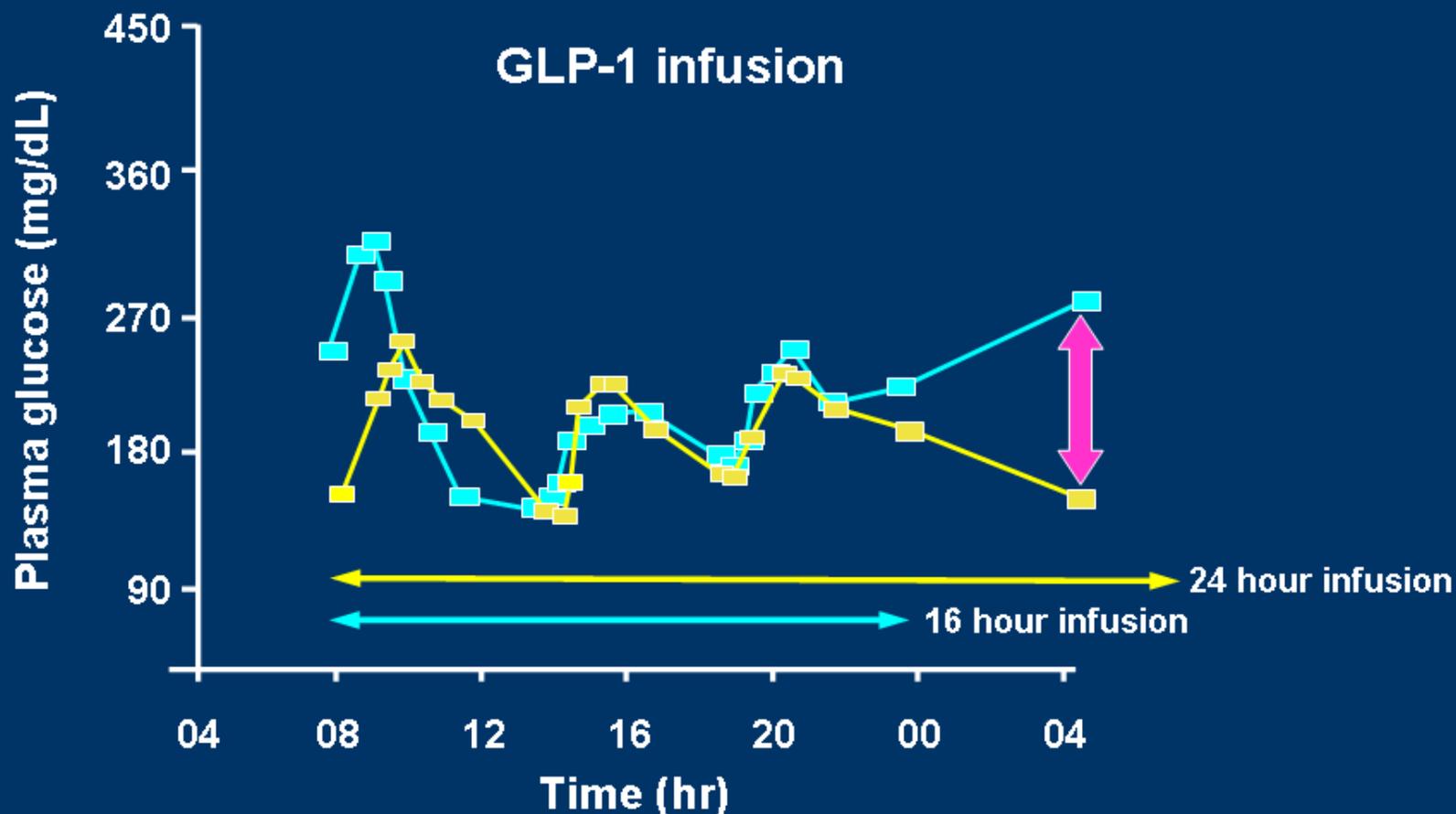
Alan C. Moses, MD

Global Chief Medical Officer

# Glucagon-like Peptide-1 – An Incretin Hormone

- **GLP-1**
  - 31 amino acid peptide
  - Secreted by L cells of the GI tract
- **Member of the incretin class of hormones**
  - Enhances insulin secretion in response to oral compared to intravenous glucose
- **Promotes glucose-dependent insulin secretion and glucose-dependent glucagon suppression**

# Importance of 24 Hour GLP-1 Exposure



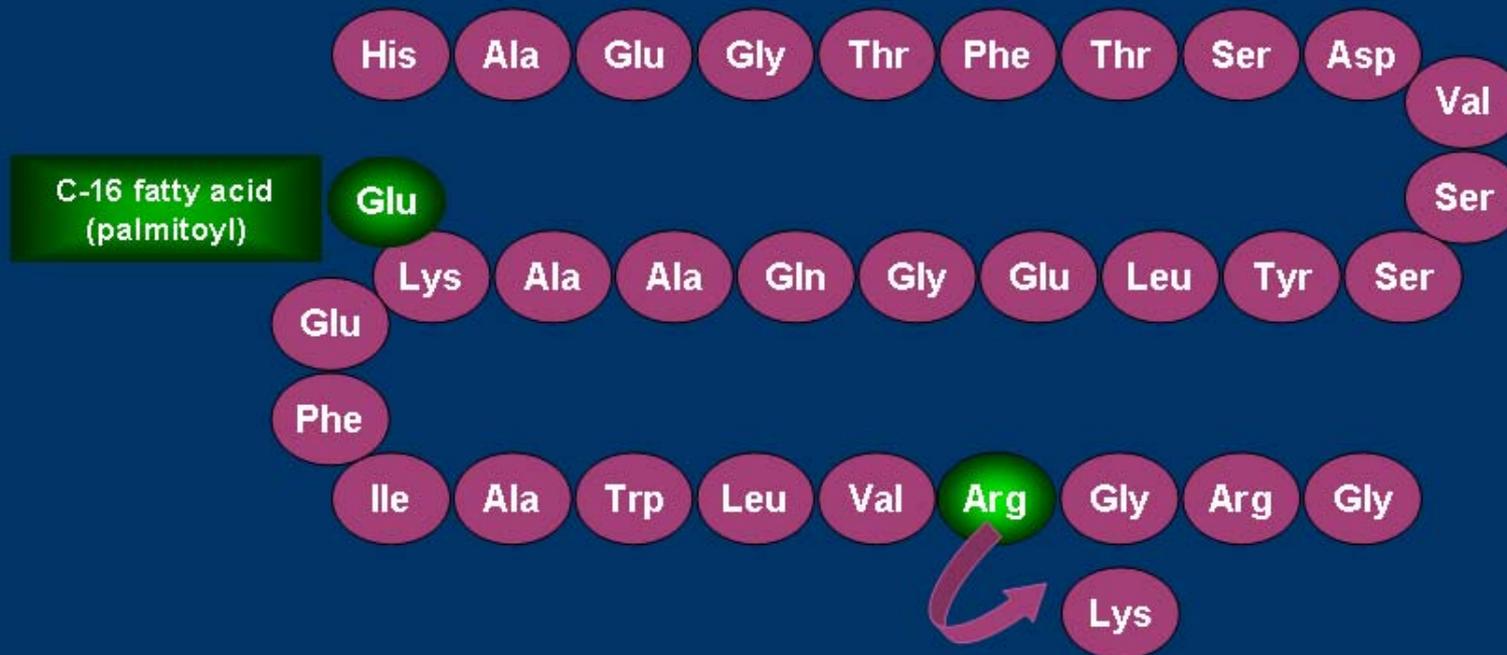
Adapted from Larsen et al. *Diabetes Care* 2001;24:1416-1421.

# Two Approaches to Enhancing Incretin Hormone Effects

- Inhibition of incretin degradation by DPP4
  - Ubiquitous enzyme with multiple targets
  - Increase levels of multiple bioactive peptides
- GLP-1 receptor agonists
  - Highly specific interaction with single GLP-1 cell surface receptor
  - Biologic effects determined by GLP-1 receptor tissue distribution and density
  - Produce pharmacologic levels of GLP-1
    - Necessary to overcome relative GLP-1 resistance in type 2 diabetes
    - Pharmacokinetics determine duration of response

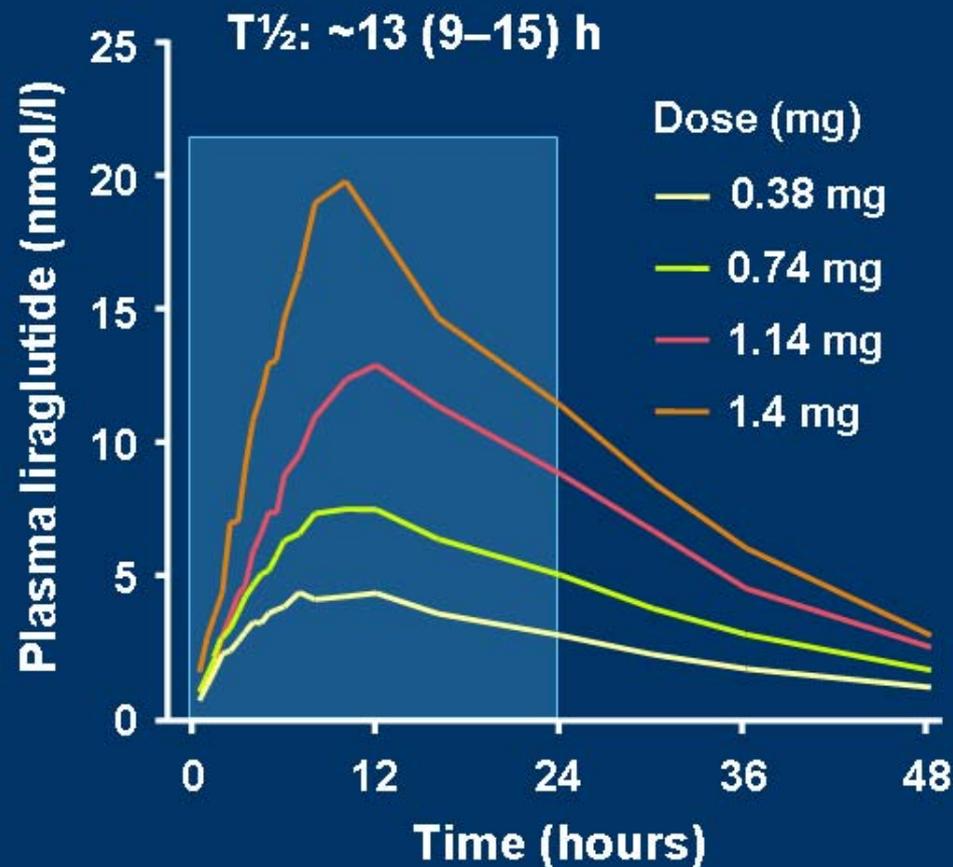
# Liraglutide, A Minimally Modified Human GLP-1 Analog

## Structural Modifications



97% amino acid homology to native GLP-1

# Liraglutide Pharmacokinetic Profile

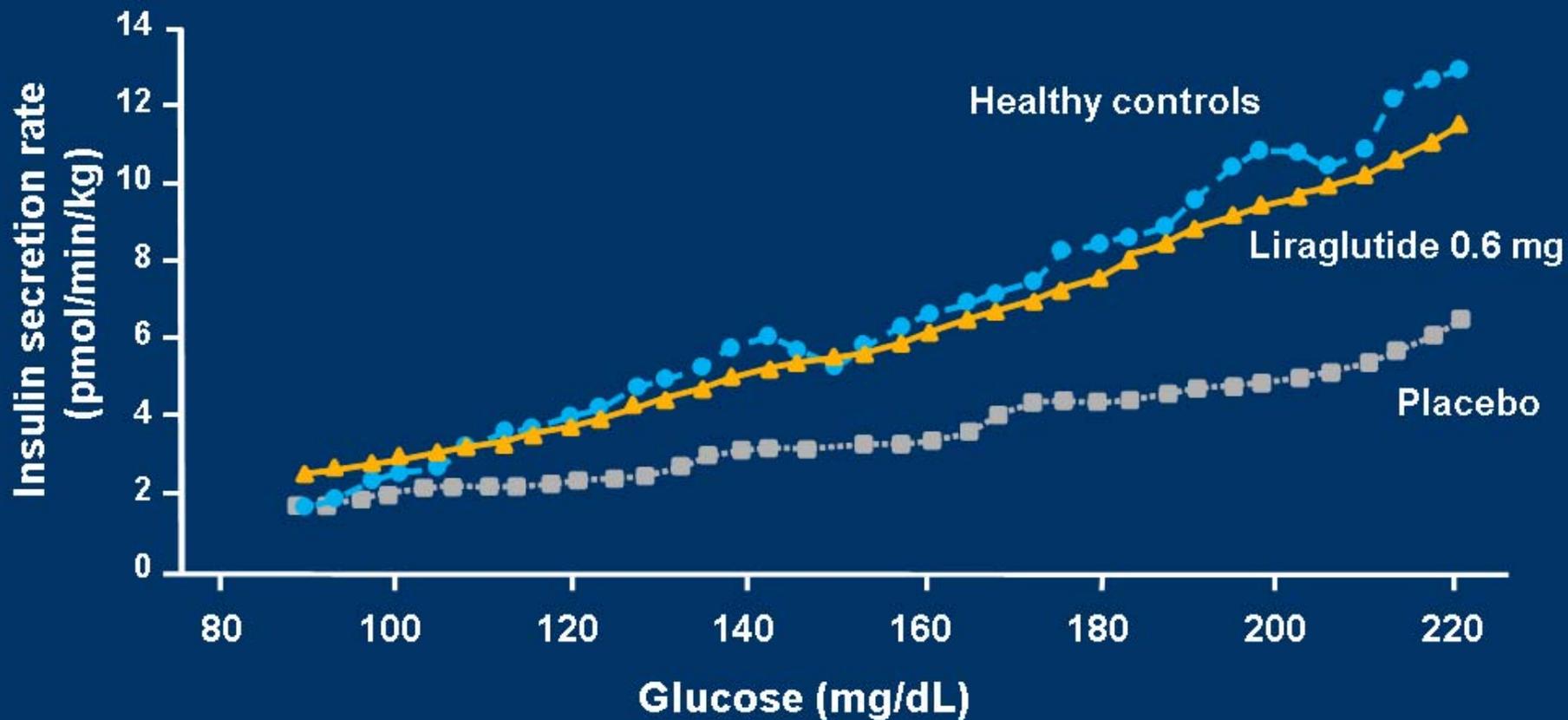


## Mechanisms underlying PK profile

- Self-association delays absorption
- Resistance to DPP4 degradation
- Albumin binding

Adapted from Elbrønd et al. *Diabetes Care* 2002;25:1398–1404.  
(n=6 for each dose)

# Liraglutide Enhances Glucose – Dependent Insulin Secretion



# Efficacy & Safety Profile of Liraglutide

Milan Zdravkovic, MD, PhD, MSc Pharm Med  
Corporate Vice President, GLP-1 Development  
Novo Nordisk

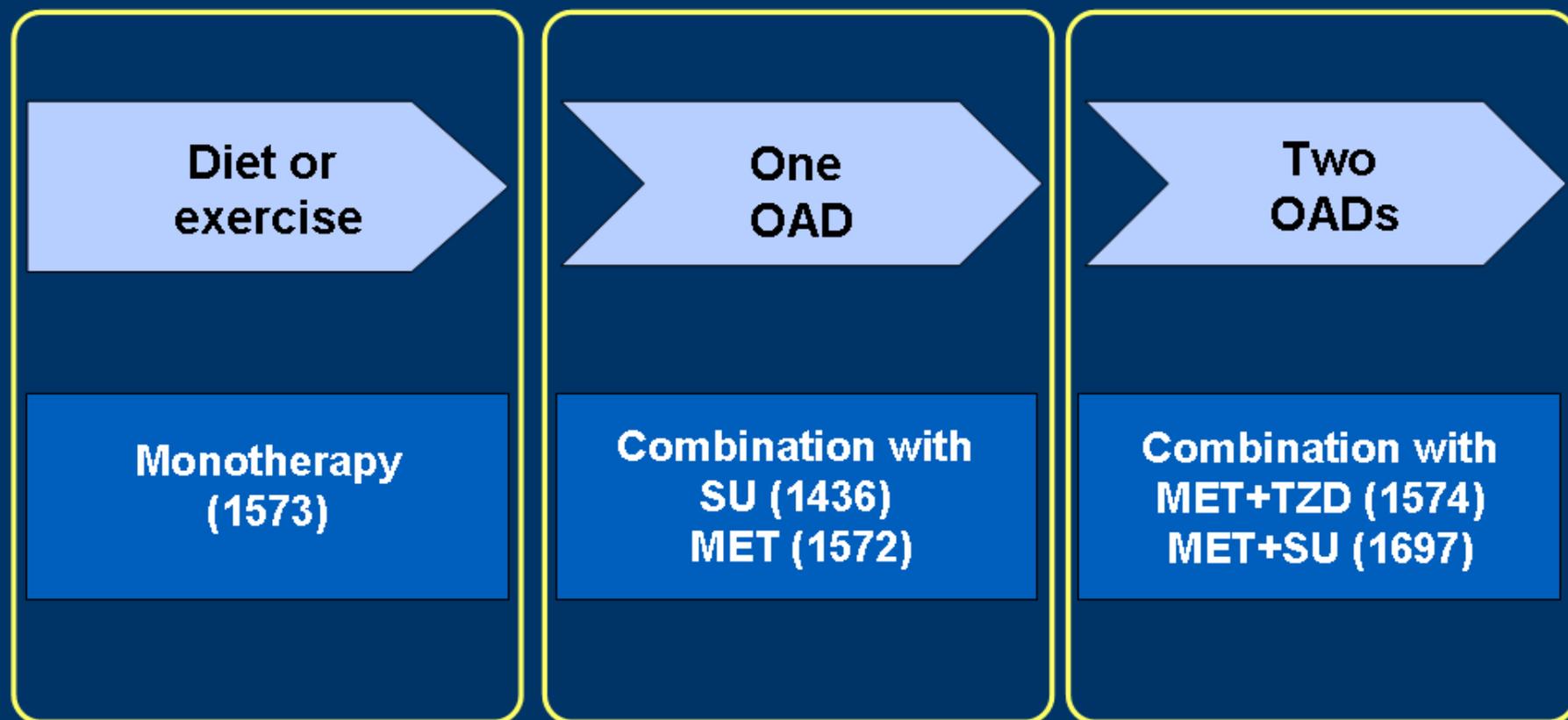
# Presentation Overview

- Background on phase 3 program
- Efficacy
  - Glycemic control
    - Hypoglycemia
  - Body weight
- Safety
  - Areas of special interest

# Liraglutide Development

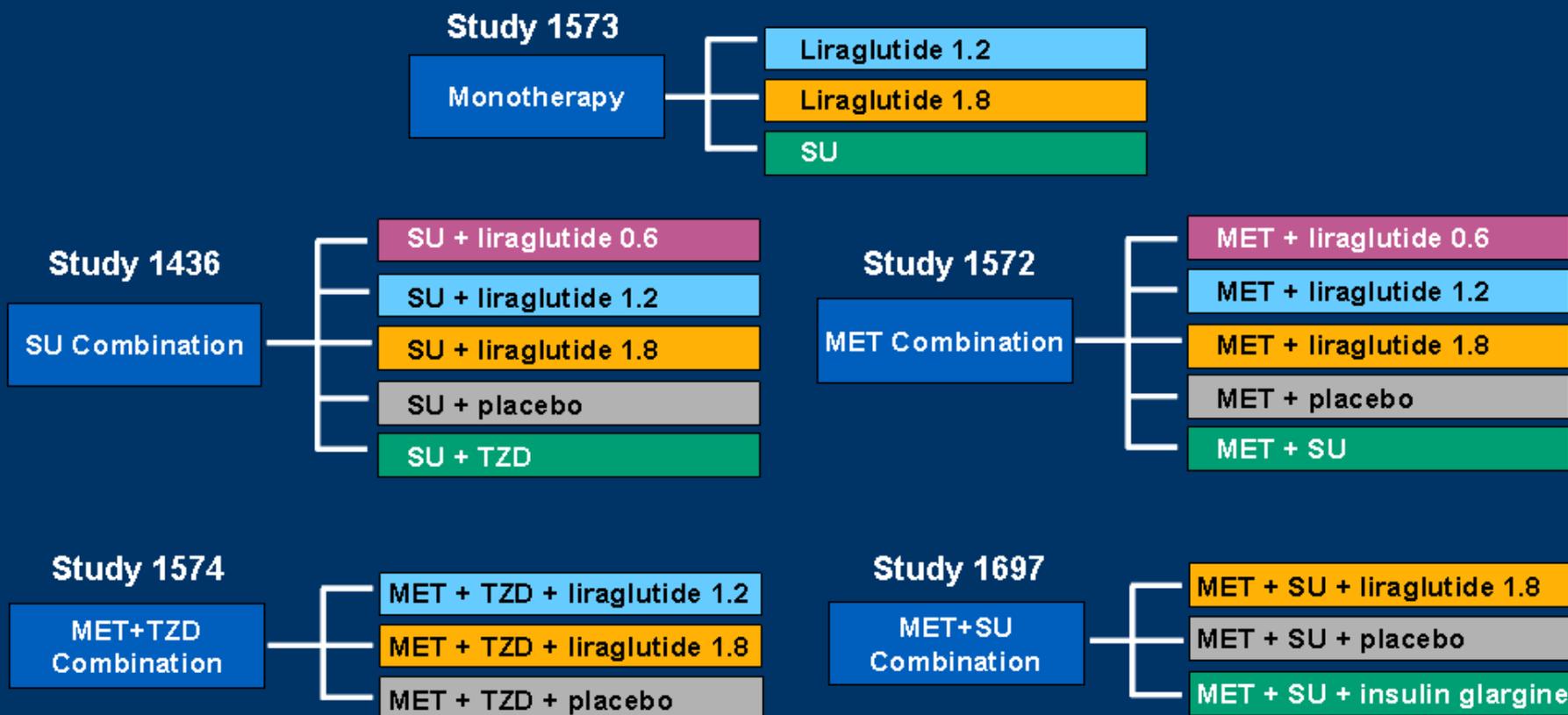
- Global development program in >40 countries
- 40 clinical trials
  - 5 phase 3 trials
- 6,885 subjects studied
  - 4,655 subjects randomized to liraglutide
  - 2,501 subjects randomized to liraglutide in Phase 3 studies

# Liraglutide Phase 3 Program from Early to Late Stage



SU: sulfonyleurea; MET: metformin; TZD: thiazolidinedione  
OAD: oral antihyperglycemic agent

# Liraglutide Phase 3 Program – Comparators and Doses



SU: sulfonyleurea; MET: metformin; TZD: thiazolidinedione (rosiglitazone)

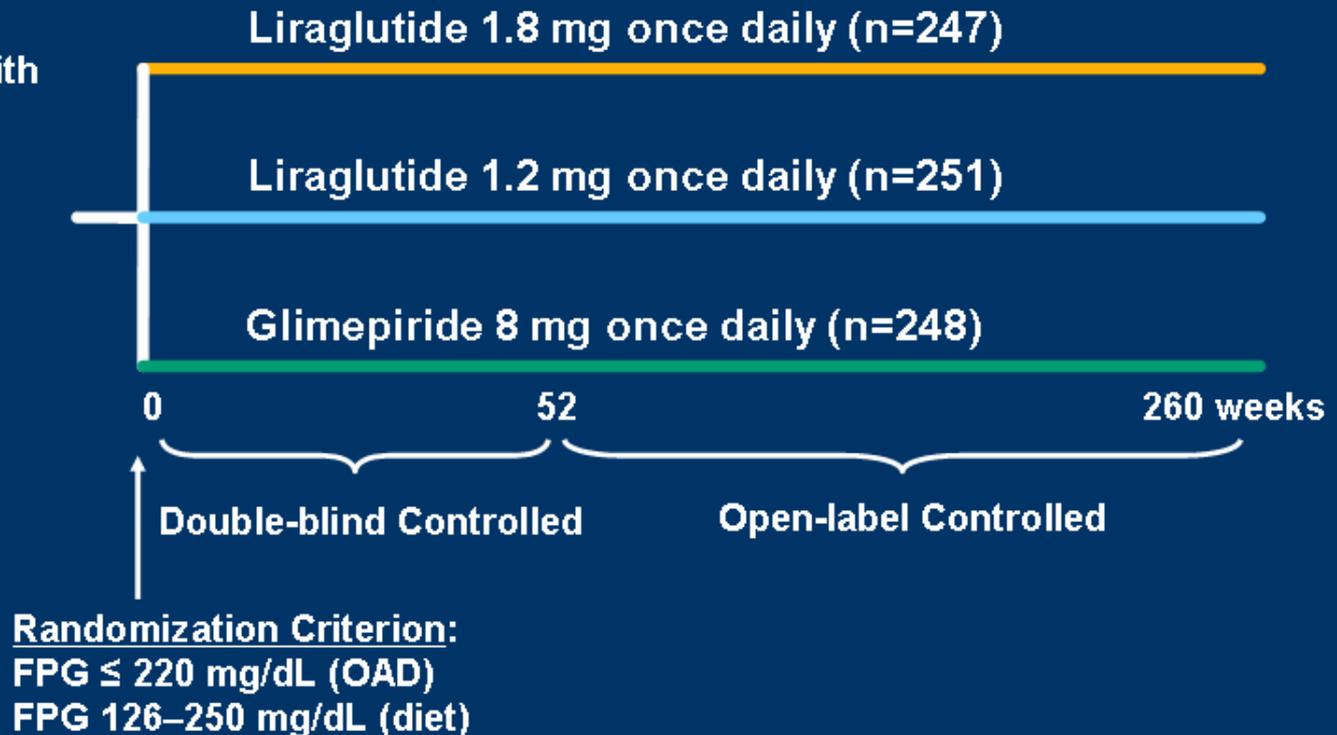
# Monotherapy Study Design (1573)

**Inclusion Criteria:**  
Adults 18–80 years with  
Type 2 diabetes

Diet/exercise  
or  
Half-maximal OAD  
monotherapy

HbA<sub>1c</sub>  
≥ 7.0%  
≤ 10.0% (OAD)  
≤ 11.0% (diet)

BMI ≤ 45 kg/m<sup>2</sup>



OADs discontinued at randomization

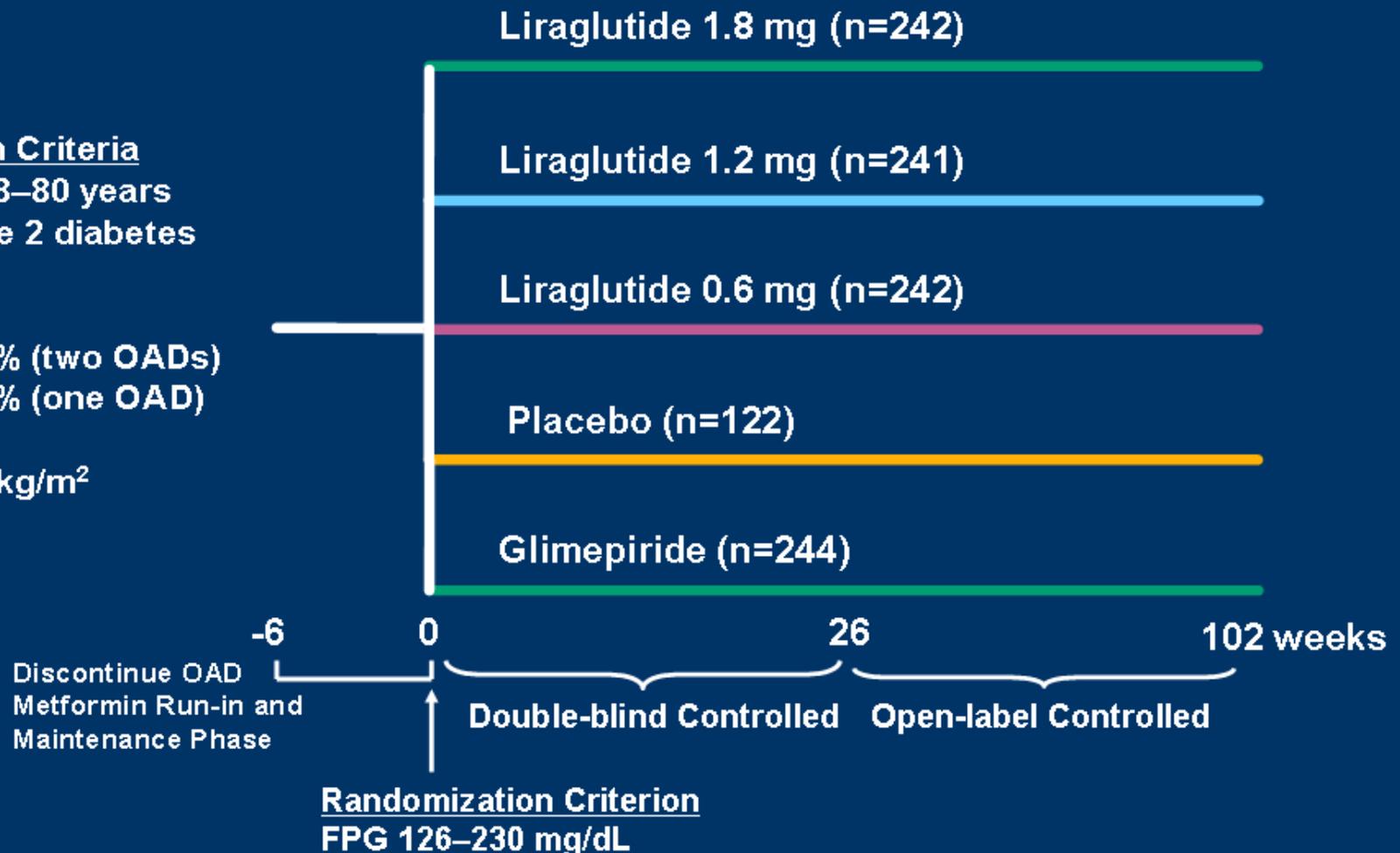
OAD: oral antihyperglycemic agent; FPG: fasting plasma glucose

# Metformin Combination Study Design (1572)

**Inclusion Criteria**  
Adults 18–80 years  
with Type 2 diabetes

**HbA<sub>1c</sub>**  
7.0–10.0% (two OADs)  
7.0–11.0% (one OAD)

**BMI ≤ 40kg/m<sup>2</sup>**



OAD: oral antihyperglycemic agent; FPG: fasting plasma glucose

# Populations and Exposure Duration

- Efficacy: Phase 3 – Study by study
- Safety: Pooled analysis across studies
  - Four Phase 3 studies were of a primary duration of 26 weeks
  - One Phase 3 study had a primary duration of 52 weeks
  - Data beyond 12 months exposure is exclusively from open label, controlled extensions
  - 703 subjects exposed for  $\geq 76$  weeks to liraglutide

# Main Inclusion/Exclusion Criteria

- Inclusion criteria
  - Subjects with Type 2 diabetes
  - HbA<sub>1c</sub> in the range from 7.0–7.5 to 10–11%
  - Age 18–80 years
  - BMI <40 to 45 kg/m<sup>2</sup>
- Exclusion criteria
  - Treatment with insulin
  - Impaired liver function
  - Impaired kidney function
  - History of myocardial infarction or heart failure

# Main Endpoints

- **Primary**
  - HbA<sub>1c</sub>
- **Secondary**
  - Body weight
  - Fasting and postprandial plasma glucose
  - Blood pressure and lipids
- **Safety endpoints**
  - Adverse events
  - Hypoglycemia
  - Safety laboratory measurements

# Study Power and Testing Procedure

- Primary endpoint – HbA<sub>1c</sub>
  - 0.5% superiority vs. placebo
  - 0.4% non-inferiority margin vs. active comparators
- Hierarchical testing procedure employed to protect overall type I error rate
  - Superiority of liraglutide vs. placebo
  - Non-inferiority of liraglutide vs. active comparator
  - Superiority of liraglutide vs. active comparator
  - Superiority of active comparator vs. placebo

# Demographics

|                                 | Monotherapy<br>(1573) | MET<br>(1572) | SU<br>(1436) | MET + TZD<br>(1574) | MET + SU<br>(1697) |
|---------------------------------|-----------------------|---------------|--------------|---------------------|--------------------|
| Subjects exposed (N)            | 745                   | 1087          | 1040         | 530                 | 576                |
| Age (years)                     | 53.0                  | 56.7          | 56.1         | 55.1                | 57.6               |
| Duration of diabetes<br>(years) | 5.4                   | 7.4           | 7.9          | 9.0                 | 9.4                |
| HbA <sub>1c</sub> (%)           | 8.2                   | 8.4           | 8.4          | 8.5                 | 8.2                |
| BMI (kg/m <sup>2</sup> )        | 33.0                  | 31.0          | 29.9         | 33.3                | 30.5               |
| Weight (kg)                     | 92.7                  | 88.6          | 81.6         | 96.3                | 85.5               |

SU: sulfonylurea; MET: metformin; TZD: thiazolidinedione (rosiglitazone)

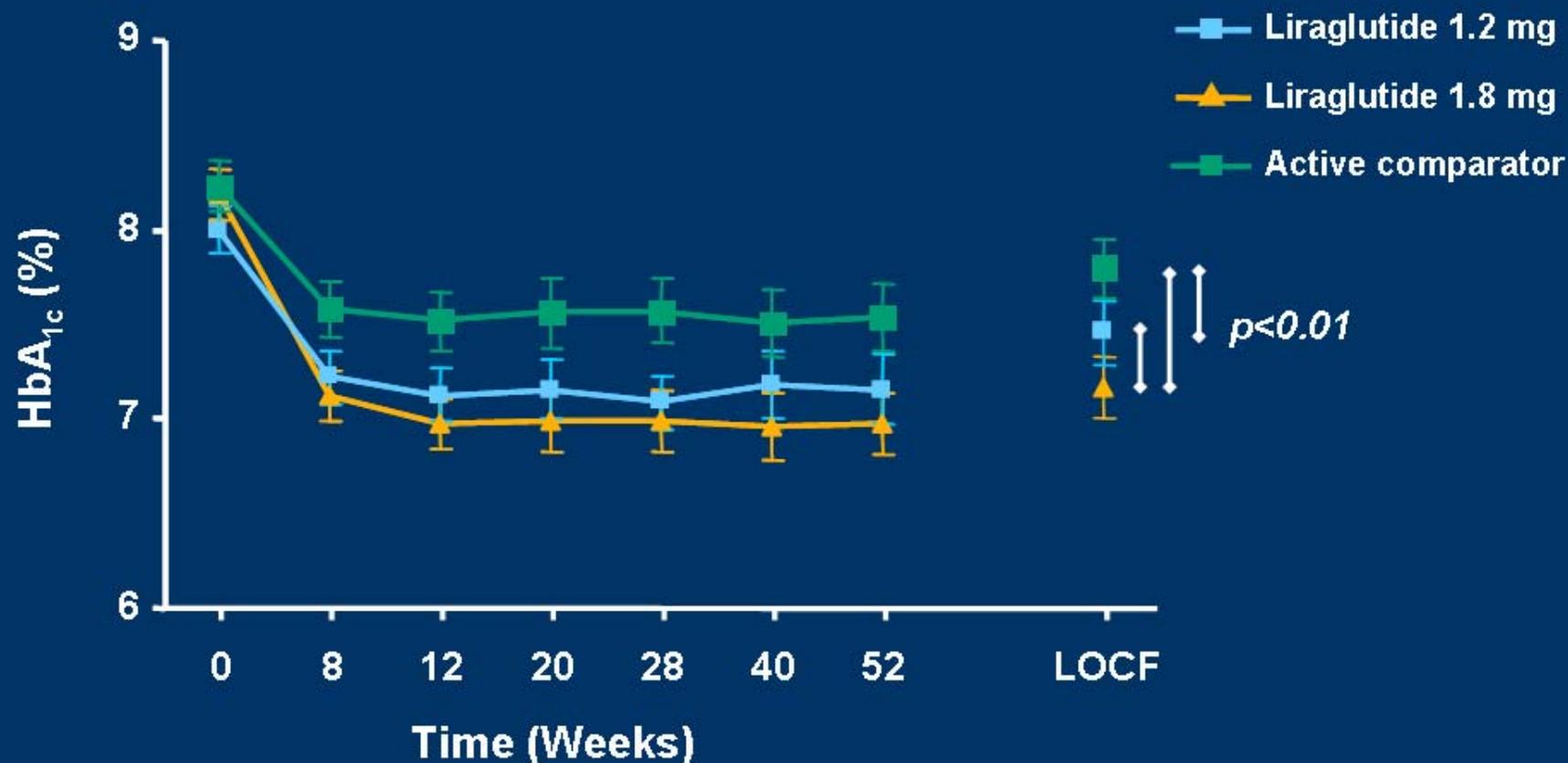
# Subject Disposition

|   | Liraglutide<br>0.6 mg  | Liraglutide<br>1.2 mg  | Liraglutide<br>1.8 mg    | Placebo                | Active<br>comparator   |
|---|------------------------|------------------------|--------------------------|------------------------|------------------------|
| <b>Safety Population %<br/>(N)</b>              | <b>100<br/>(N=475)</b> | <b>100<br/>(N=896)</b> | <b>100<br/>(N=1,130)</b> | <b>100<br/>(N=524)</b> | <b>100<br/>(N=953)</b> |
| <b>Withdrawals (%)</b>                          | 12.4                   | 21.0                   | 18.9                     | 28.6                   | 18.7                   |
| <b>Adverse events (%)</b>                       | 3.4                    | 7.7                    | 8.2                      | 2.9                    | 3.7                    |
| <b>Non-compliance with<br/>the protocol (%)</b> | 1.1                    | 2.7                    | 2.0                      | 2.1                    | 2.0                    |
| <b>Ineffective therapy (%)</b>                  | 6.5                    | 3.8                    | 3.0                      | 17.4                   | 5.3                    |
| <b>Other (%)</b>                                | 1.5                    | 6.8                    | 5.7                      | 6.3                    | 7.8                    |
| <b>Completers (%)</b>                           | 87.6                   | 79.0                   | 81.2                     | 71.4                   | 81.3                   |

# Presentation Overview

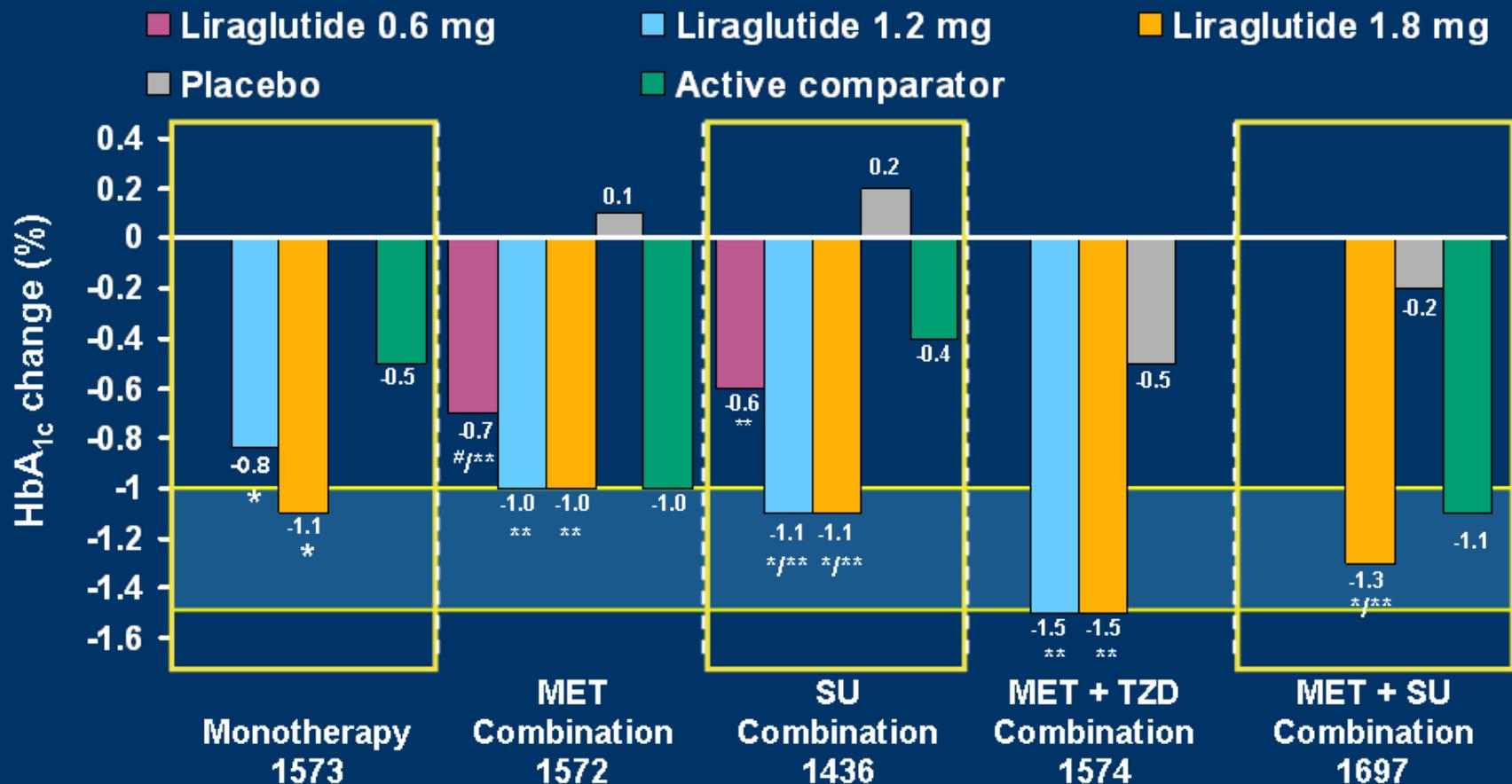
- Background on phase 3 program
- **Efficacy**
  - Glycemic control
    - Hypoglycemia
  - Body weight
- **Safety**
  - Areas of special interest

# HbA<sub>1c</sub> Over Time – Monotherapy Study (1573)



Mean  $\pm$  2xSEM; ITT population

# HbA<sub>1c</sub> Change from Baseline



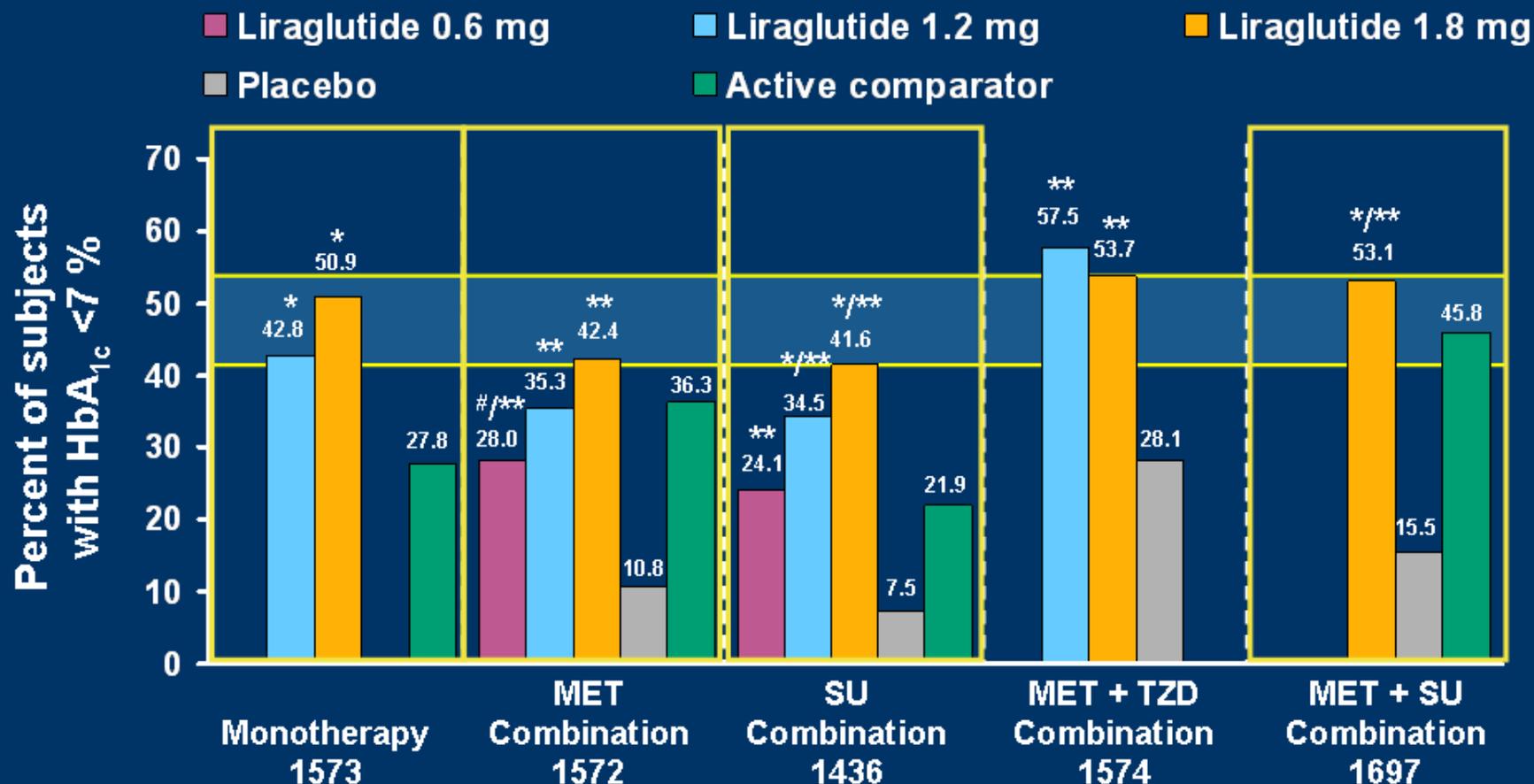
\*Liraglutide significantly lower than active comparator

#Active comparator significantly lower than liraglutide

\*\*Liraglutide significantly different from placebo

Estimated changes LOCF data set (Last Observation Carried Forward); SU: sulfonylurea; MET: metformin; TZD: thiazolidinedione

# Percentage of Subjects Reaching ADA Target (HbA<sub>1c</sub> <7.0%)



\*Liraglutide significantly higher than active comparator

#Active comparator significantly higher than liraglutide

\*\*Liraglutide significantly higher than placebo

Estimated changes LOCF data set (Last Observation Carried Forward) SU: sulfonylurea; MET: metformin; TZD: thiazolidinedione

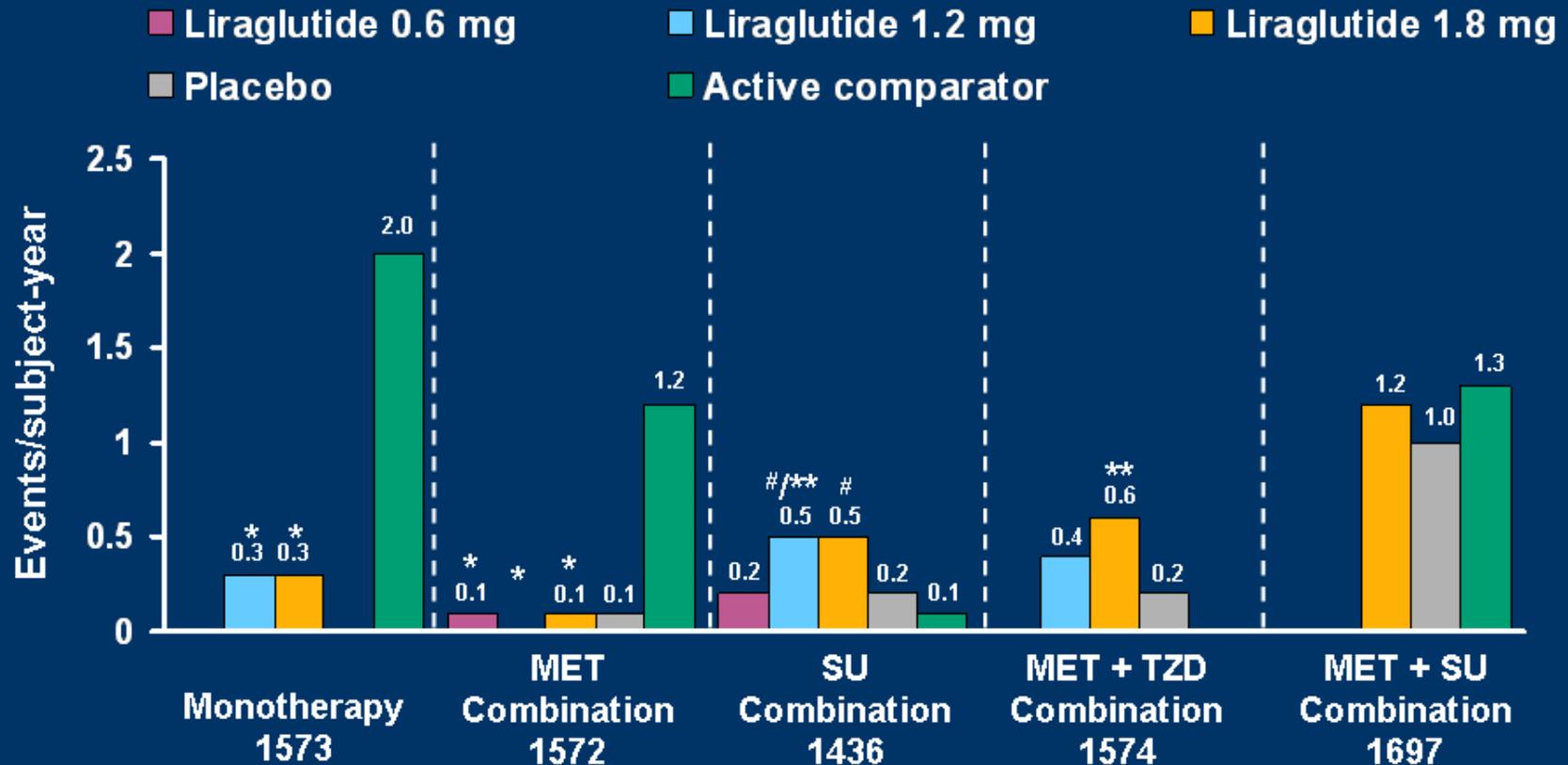
# Fasting and Postprandial Glycemic Control

- The 24 hour action profile reduces both fasting and postprandial glucose levels
- Significant lowering of both parameters vs. placebo
- In monotherapy and SU combination therapy significant difference also seen vs. active comparators
  - Glimepiride
  - Rosiglitazone (in combination with a SU)

# Presentation Overview

- Background on phase 3 program
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  - Glycemic control
    - Hypoglycemia
  - Body weight
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# Rates of Minor Hypoglycemic Episodes



\*Liraglutide significantly lower than active comparator

#Liraglutide significantly higher than active comparator

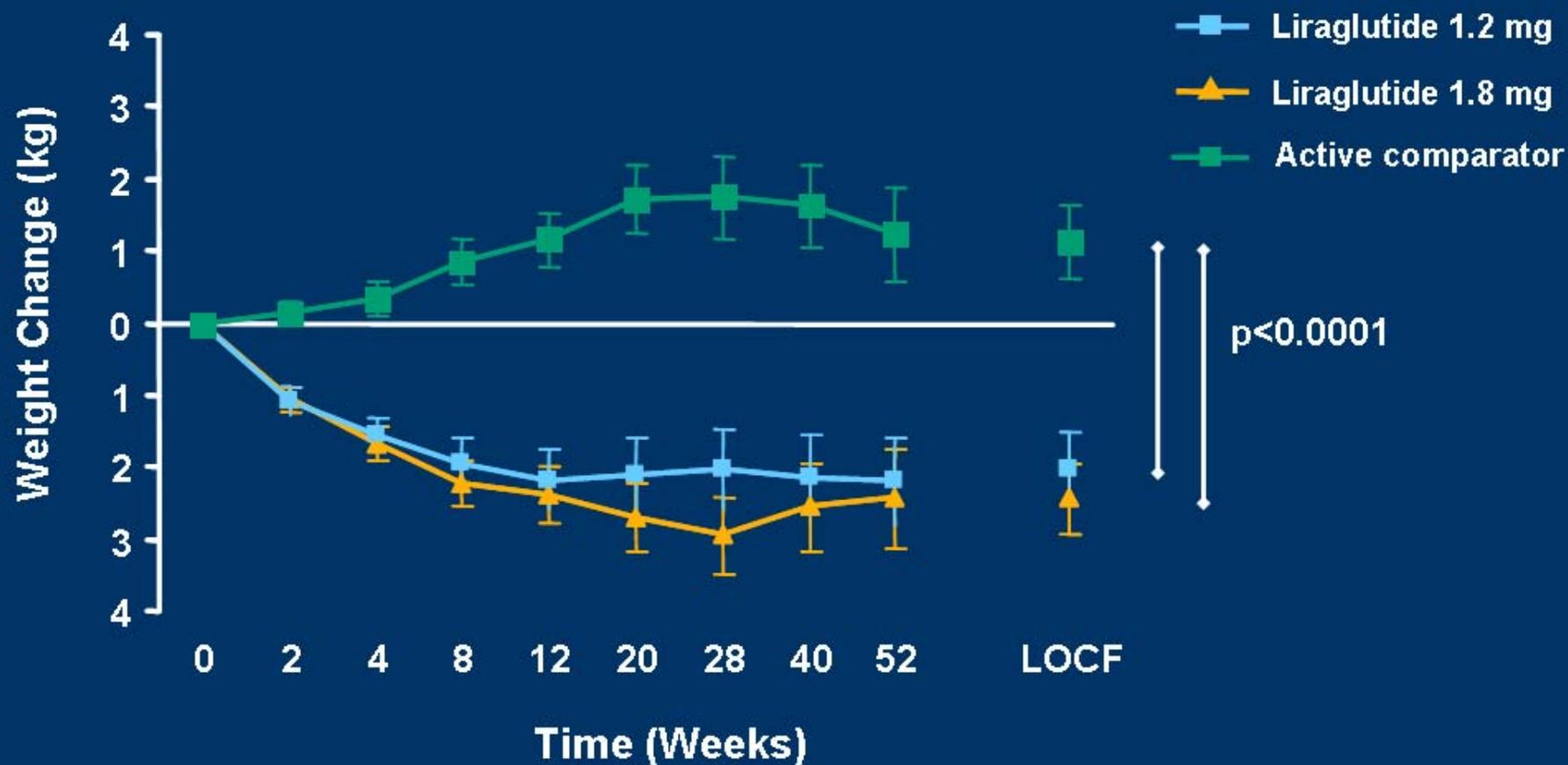
\*\*Liraglutide significantly higher than placebo

SU: sulfonylurea; MET: metformin; TZD: thiazolidinedione (rosiglitazone)

# Presentation Overview

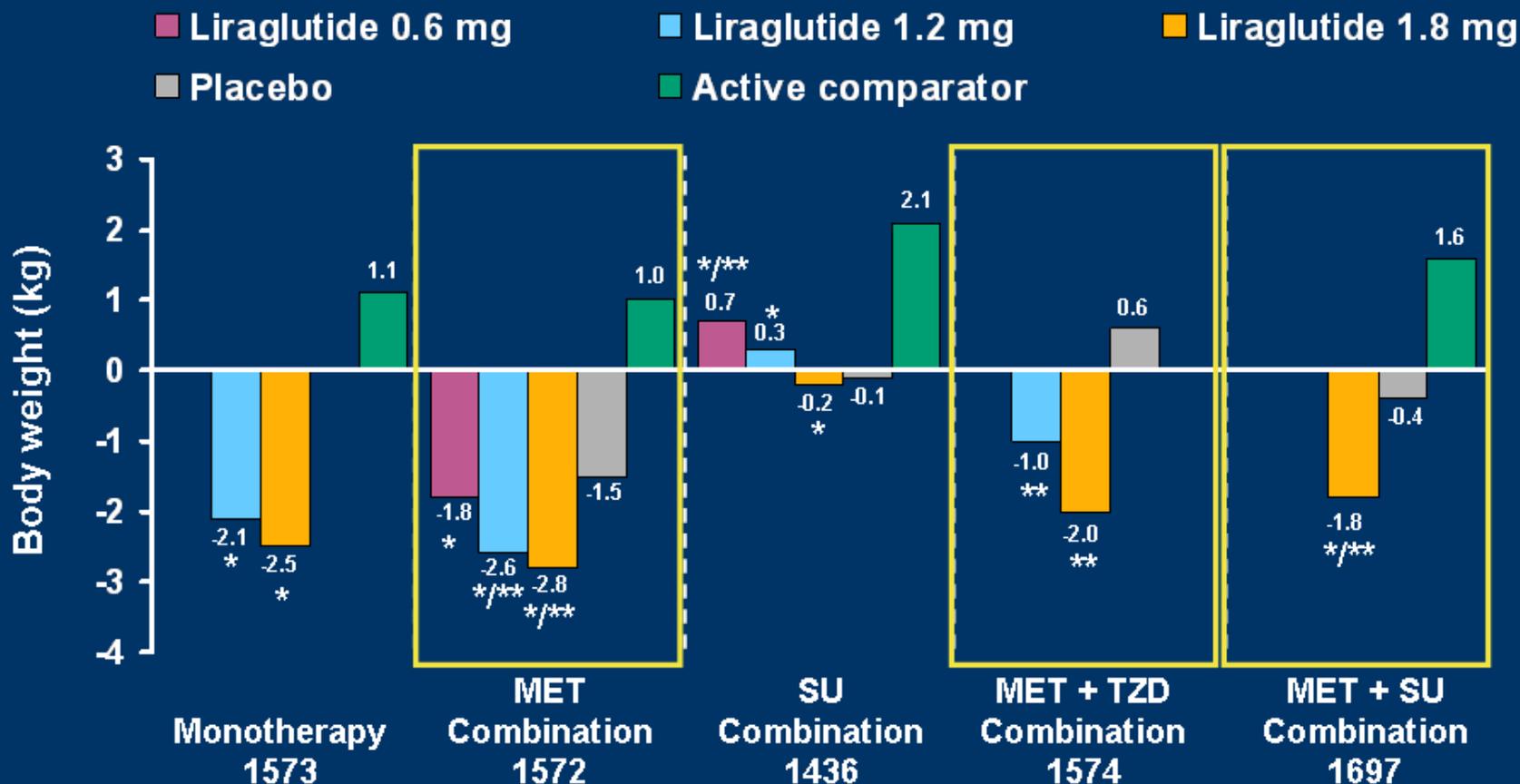
- Background on phase 3 program
- Efficacy
  - Glycemic control
    - Hypoglycemia
  - **Body weight**
- Safety
  - Areas of special interest

# Weight Change Over Time – Monotherapy Study (1573)



Mean  $\pm$  2xSEM; ITT population

# Body Weight Change from Baseline

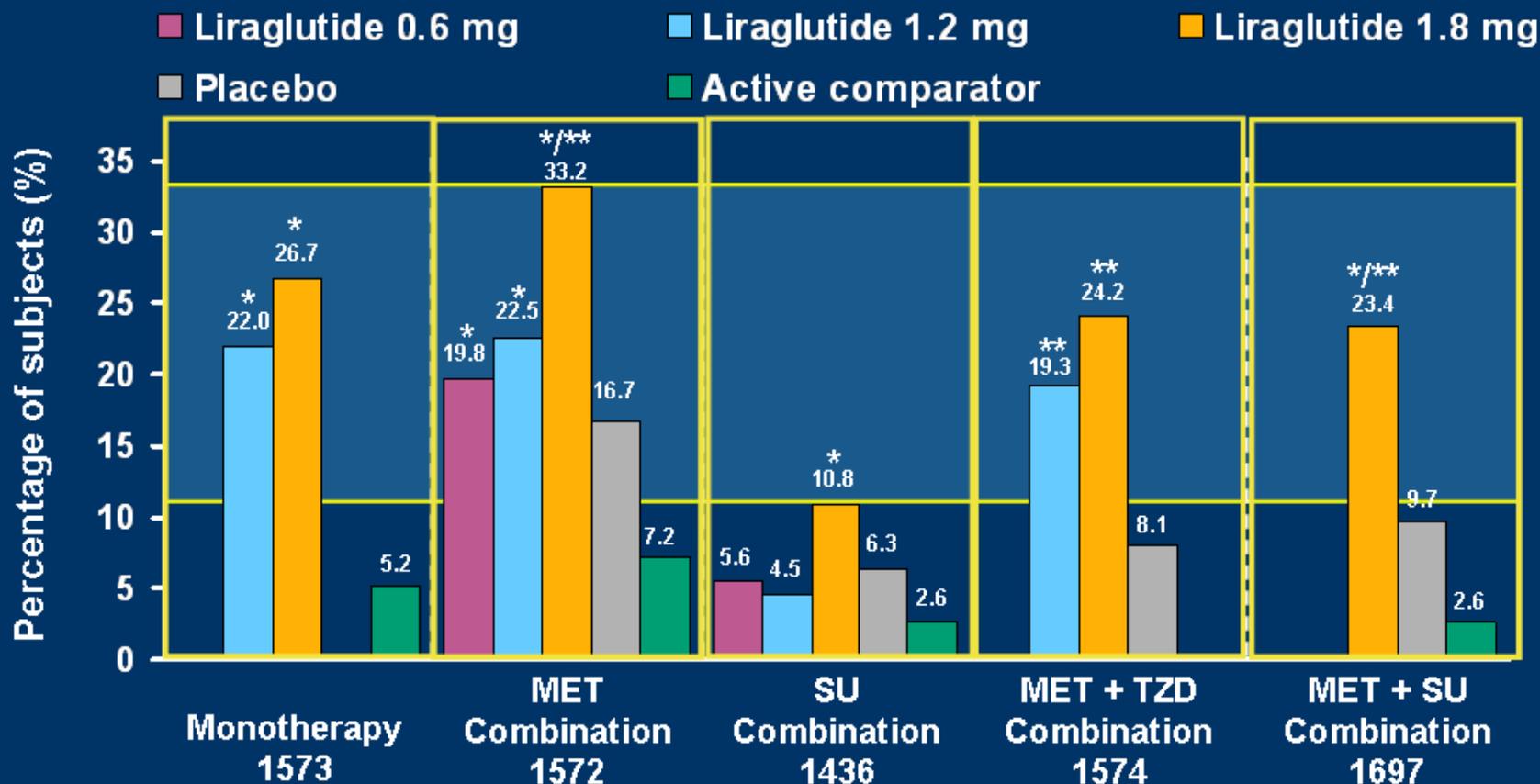


\*Liraglutide significantly different from active comparator

\*\*Liraglutide significantly different from placebo

Estimated changes LOCF data set; SU: sulfonylurea; MET: metformin; TZD: thiazolidinedione (rosiglitazone)

# Percent of Subjects Who Had Weight Loss of 5% or More



\*Liraglutide significantly higher than active comparator

\*\*Liraglutide significantly higher than placebo

Estimated changes LOCF data set; SU: sulfonylurea; MET: metformin; TZD: thiazolidinedione (rosiglitazone)

# Efficacy Summary

- Glycemic control (HbA<sub>1c</sub>) – primary endpoint
  - Significant reductions
    - Versus placebo
    - In monotherapy vs. glimepiride
    - In combination with SU vs. rosiglitazone+SU
    - In combination with MET+SU vs. insulin glargine+MET+SU (difference within the non-inferiority margin)
- Low risk of hypoglycemia
- Additional effect – secondary endpoint
  - Weight reduction

# Presentation Overview

- Background on phase 3 program
- Efficacy
  - Glycemic control
    - Hypoglycemia
  - Body weight
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# Preclinical Program

- Standard preclinical safety program
- Liraglutide well-tolerated
- Effects generally consistent with pharmacology

# Preclinical Carcinogenicity Assessment

- Liraglutide not genotoxic
  - No genotoxicity *in vitro*
  - No genotoxicity *in vivo*
- Life-time bioassays in mice and rats
  - Histopathology including >40 tissues
  - No general increase in tumor incidence
  - Two tumor types evaluated further

# Dorsal Subcutaneous Sarcomas in Mice

- Observed in high-dose male mice
- GLP-1 receptor not described in cell types related to sarcomas
- Predisposing factors present\*
  - Repeated s.c. injections
  - Microchip identification implants

\*References: Blanchard et al, 1999; Grasso, 1987; Grasso et al., 1971; Grasso et al, 1991; Greaves, 2007; Hildebrand et al, 1991; Elcock et al, 2001; Le Calvez et al, 2006; Tillmann et al, 1997.

# Evaluation – Dorsal Subcutaneous Sarcomas

- Single species finding
- Single sex finding
- Increased incidence only at highest dose
  - Corresponding to >30 fold human dose
- Known predisposing factors
- Not considered of clinical relevance

# Mouse Carcinogenicity Study – C-cell Proliferative Findings

| Dose, mg/kg/day<br>(Exposure ratio <sup>a</sup> ) | Males    |               |              |             |             | Females  |               |              |             |             |
|---|----------|---------------|--------------|-------------|-------------|----------|---------------|--------------|-------------|-------------|
|   | 0<br>(0) | 0.03<br>(0.2) | 0.2<br>(1.6) | 1.0<br>(13) | 3.0<br>(36) | 0<br>(0) | 0.03<br>(0.2) | 0.2<br>(1.6) | 1.0<br>(13) | 3.0<br>(36) |
| Focal C-cell<br>hyperplasia (%)                   | 0        | 0             | 1.5          | 16***       | 38***       | 0        | 0             | 10**         | 15***       | 29***       |
| C-cell adenoma<br>(%)                             | 0        | 0             | 0            | 13***       | 19***       | 0        | 0             | 0            | 6*          | 20***       |
| C-cell carcinoma<br>(%)                           | 0        | 0             | 0            | 0           | 0           | 0        | 0             | 0            | 0           | 2.6         |

<sup>a</sup>Exposure ratio to human AUC at 1.8 mg  
\*P<0.05, \*\*P<0.001, \*\*\*P<0.001; N=65-79/sex/group

# Rat Carcinogenicity Study – C-cell Proliferative Findings

| Dose, mg/kg/day<br>(Exposure ratio <sup>a</sup> ) | Males    |                |               |               | Females  |                |               |               |
|---|----------|----------------|---------------|---------------|----------|----------------|---------------|---------------|
|   | 0<br>(0) | 0.075<br>(0.5) | 0.25<br>(2.4) | 0.75<br>(8.1) | 0<br>(0) | 0.075<br>(0.5) | 0.25<br>(2.4) | 0.75<br>(8.1) |
| Focal C-cell hyperplasia (%)                      | 22       | 29             | 40            | 48*           | 28       | 29             | 55**          | 48            |
| C-cell adenoma (%)                                | 12       | 16             | 42**          | 46***         | 10       | 27*            | 33**          | 56***         |
| C-cell carcinoma (%)                              | 2        | 8              | 6             | 14**          | 0        | 0              | 4             | 6             |

<sup>a</sup>Exposure ratio to human AUC at 1.8 mg

\*P<0.05, \*\*P<0.01, \*\*\*P<0.001; N=50/sex/group

# Thyroid Follicular Cells and C-cells

|                         | Embryologic Origin | Possible Malignancy | Endocrine Product |
|-------------------------|--------------------|---------------------|-------------------|
| <i>Follicular Cells</i> | Endodermal         | Papillary carcinoma | T4, T3            |
| <i>C-cells</i>          | Ectodermal         | Medullary carcinoma | Calcitonin        |



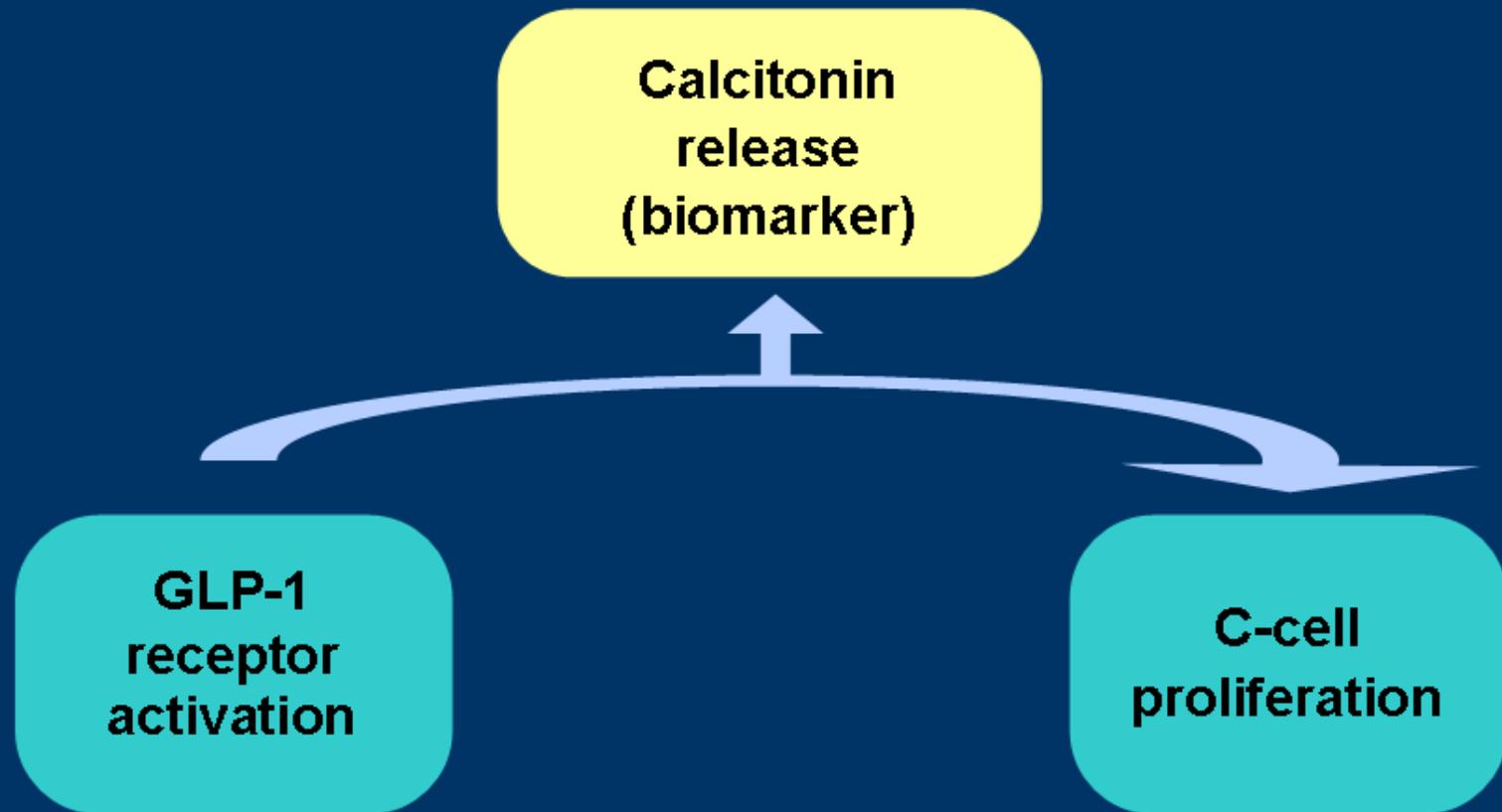
Thyroid histology

Follicular cells  
C-cells

# Mechanistic C-cell Studies

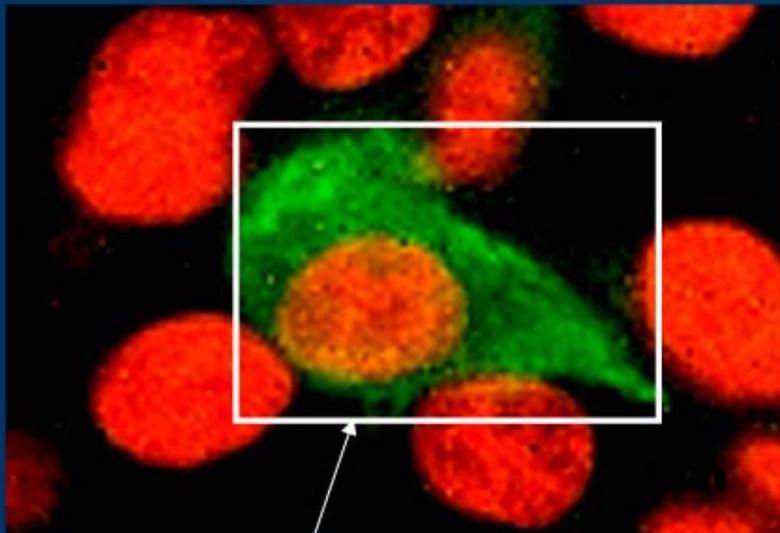
- More than 30 nonclinical studies performed
- *In vitro*
  - GLP-1 receptor studies in C-cells
  - General and specific receptor screening studies
  - Mitogenicity studies in C-cell lines
- *In vivo*
  - C-cell studies in rodents and non-human primates
  - Evaluation of early and long-term calcitonin response
  - Highly sensitive evaluation of C-cell proliferation

# Mode-of-Action – Rodent C-cell Proliferation



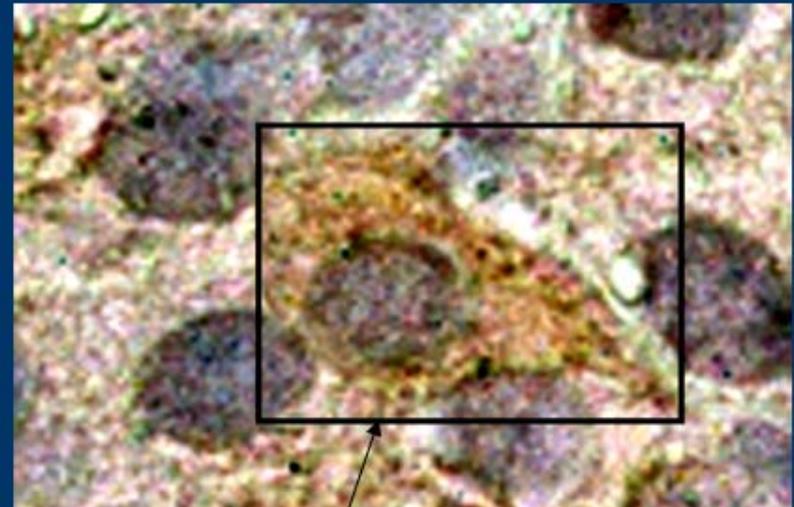
# GLP-1 Receptor Localization in Rat Thyroid

- GLP-1 receptor confined to C-cells in rats



**C-cell (calcitonin, green)**

Orange: cell nucleus



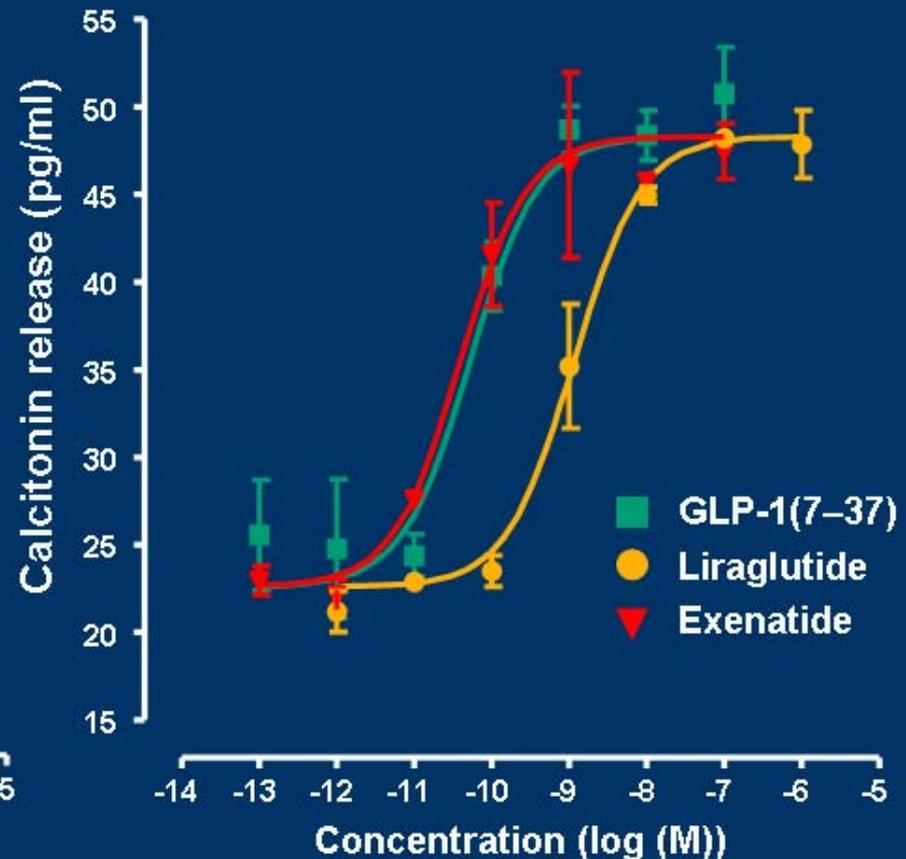
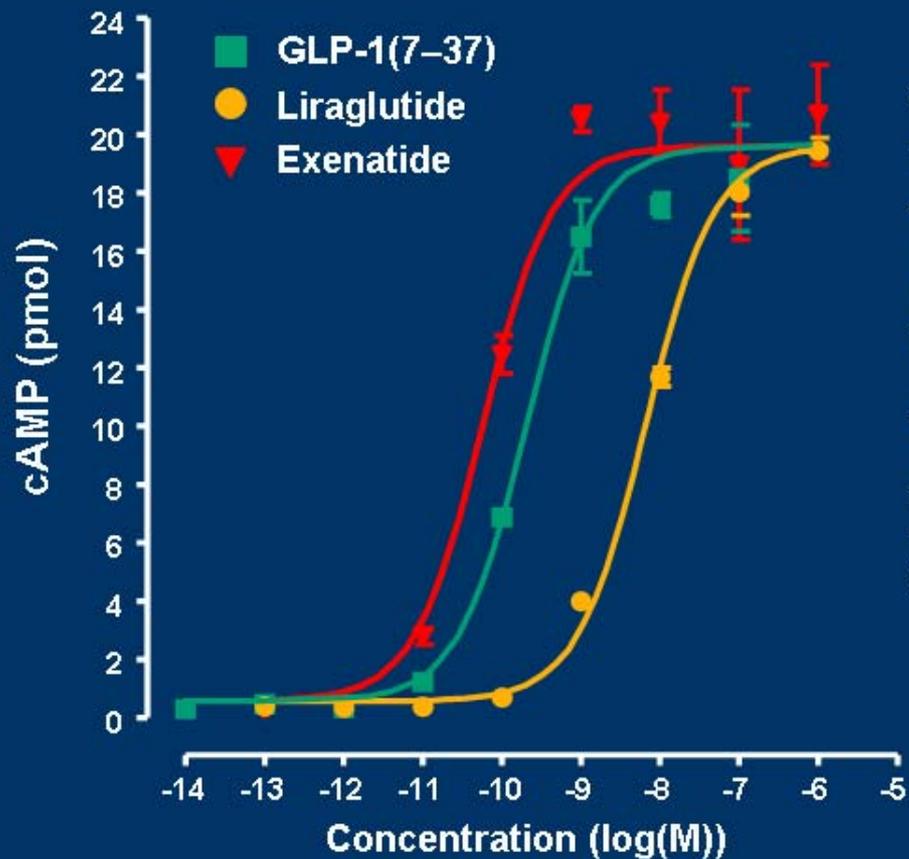
**GLP-1 receptor (brown)**

Blue: cell nucleus

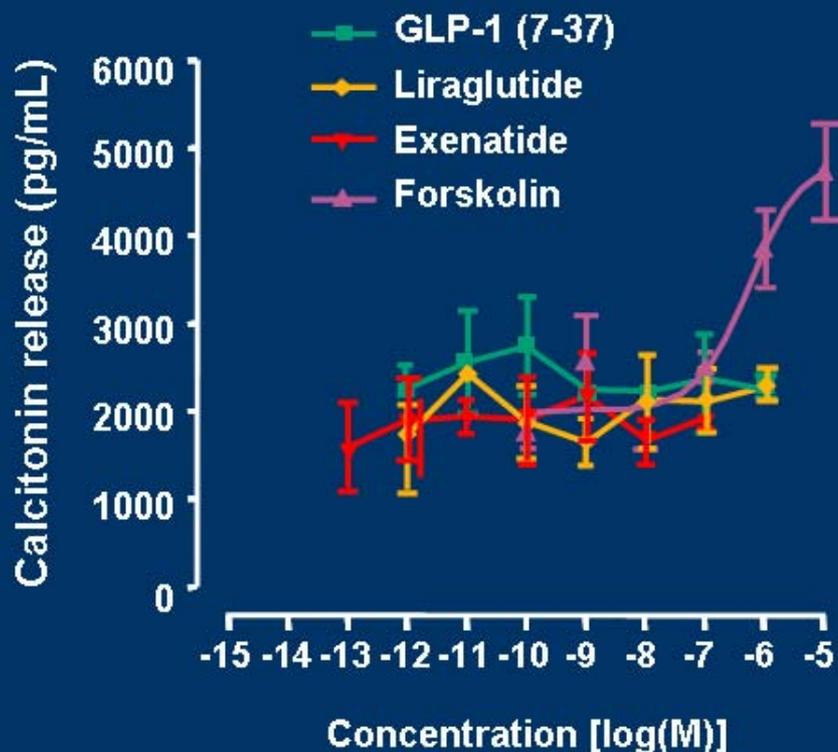
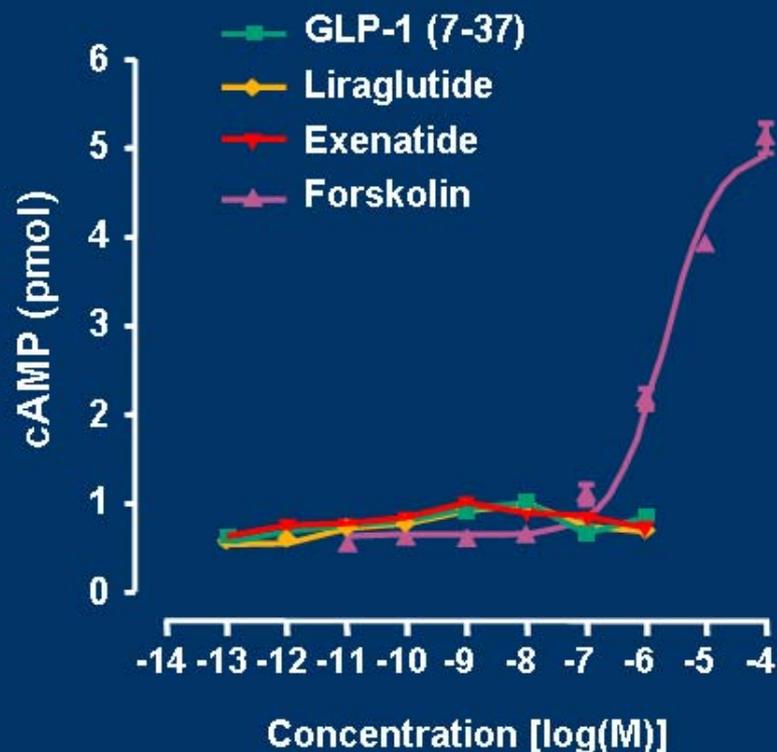
# GLP-1 Receptor Presence in Thyroid

- Immunohistochemistry GLP-1R specific
  - Documented by appropriate controls
- Data confirmed by additional methods
  - *In situ* hybridization
  - *In situ* ligand binding / autoradiography
- Data consistent with literature

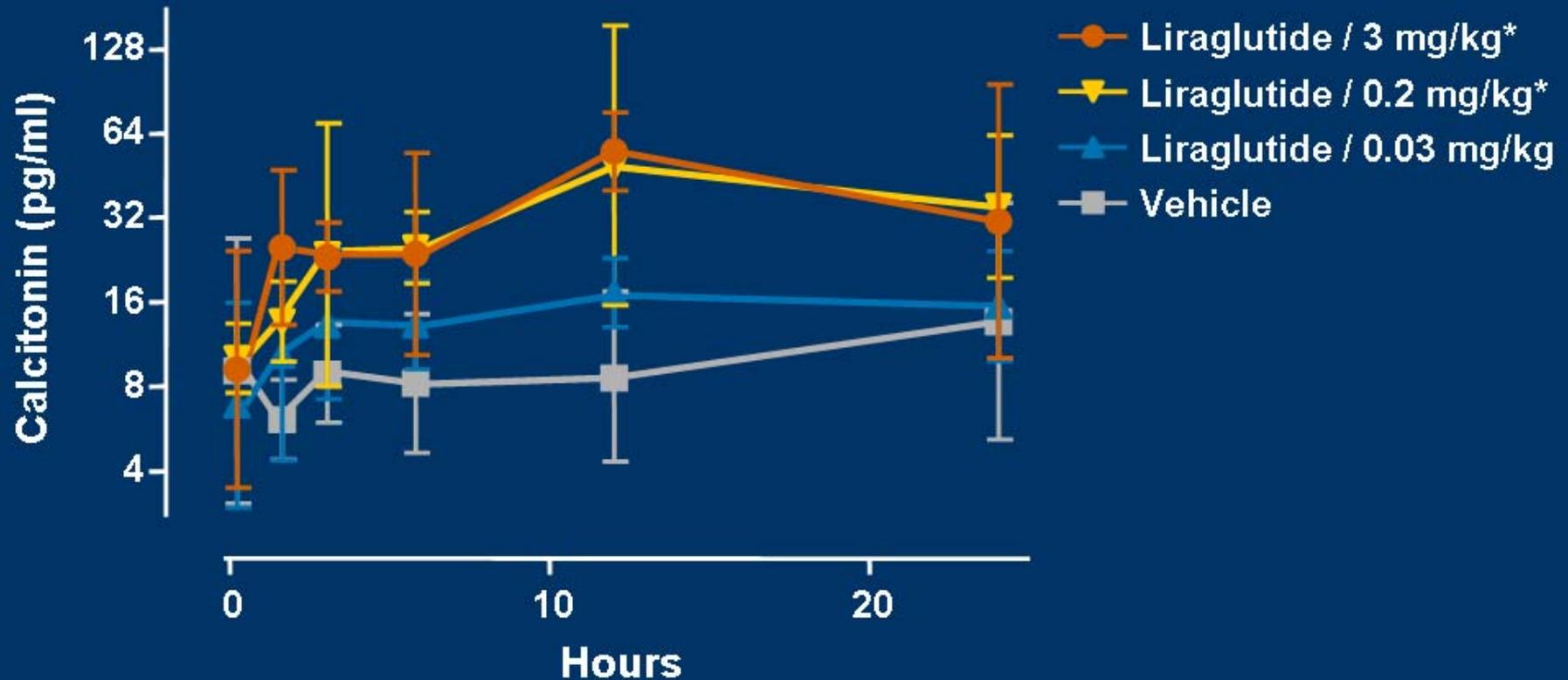
# GLP-1 Receptor Activation and Calcitonin Release in Rat C-cell Line



# No GLP-1 Receptor Activation or Calcitonin Release in Human C-cell Line

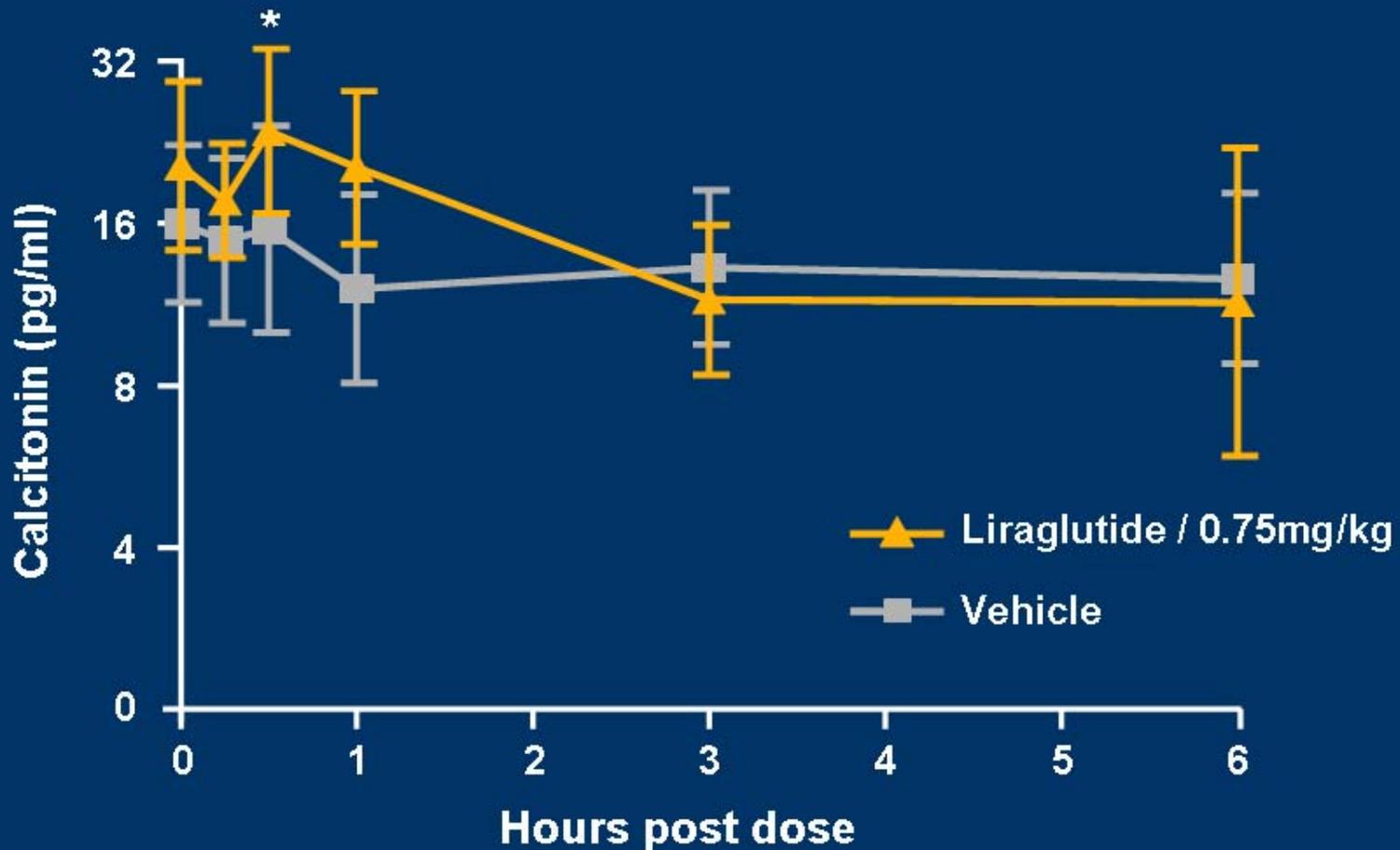


# Acute Calcitonin Release in Mice



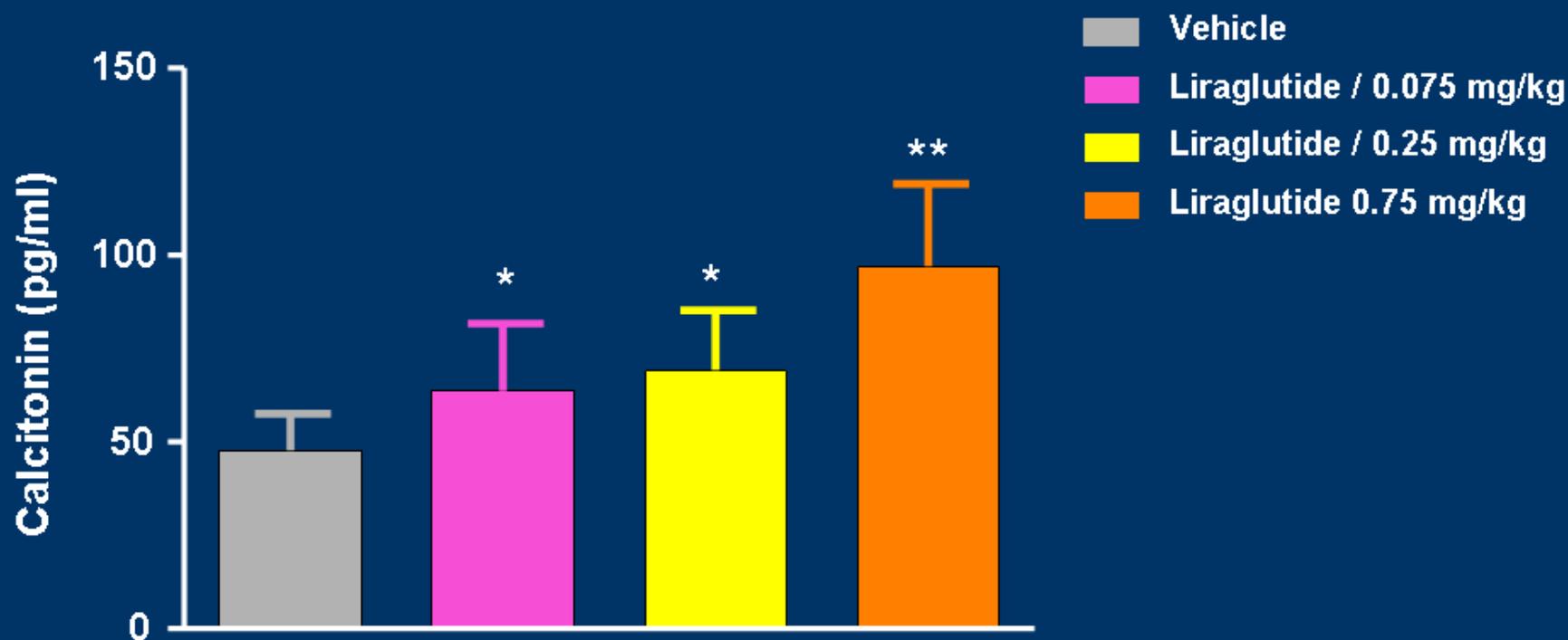
Calcitonin geometric mean and 95%CI; N=6 / group / time;  
\*p<0.05

# Acute Calcitonin Release in Rats



•Calcitonin geometric mean and 95%CI;  
N=10/group; \*p<0.05

# Calcitonin Release in Rats After 4 Weeks

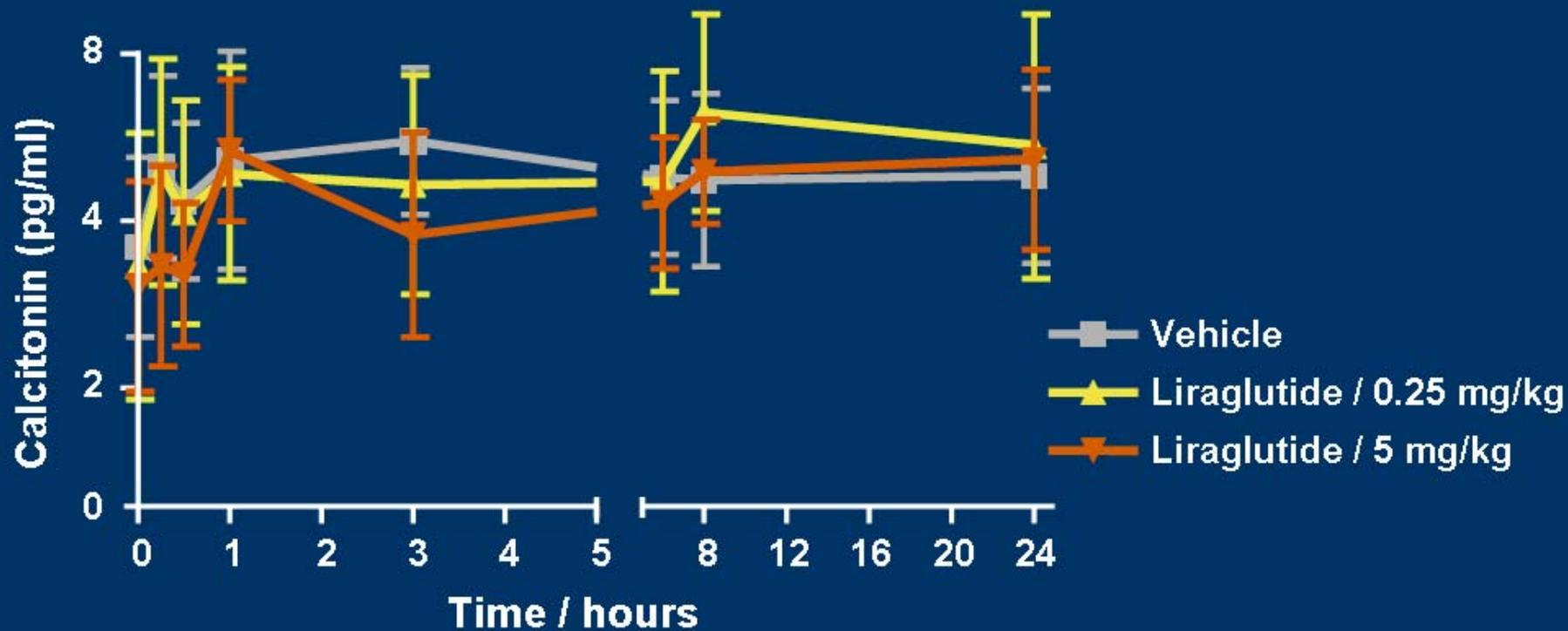


Plasma calcitonin (geometric mean and 95% CI; 3 hours after dosing in aged rats)  
N = 42-45/group; \*/\*\* p<0.05/0.01 compared to vehicle

# Calcitonin – A Biomarker in Rodents

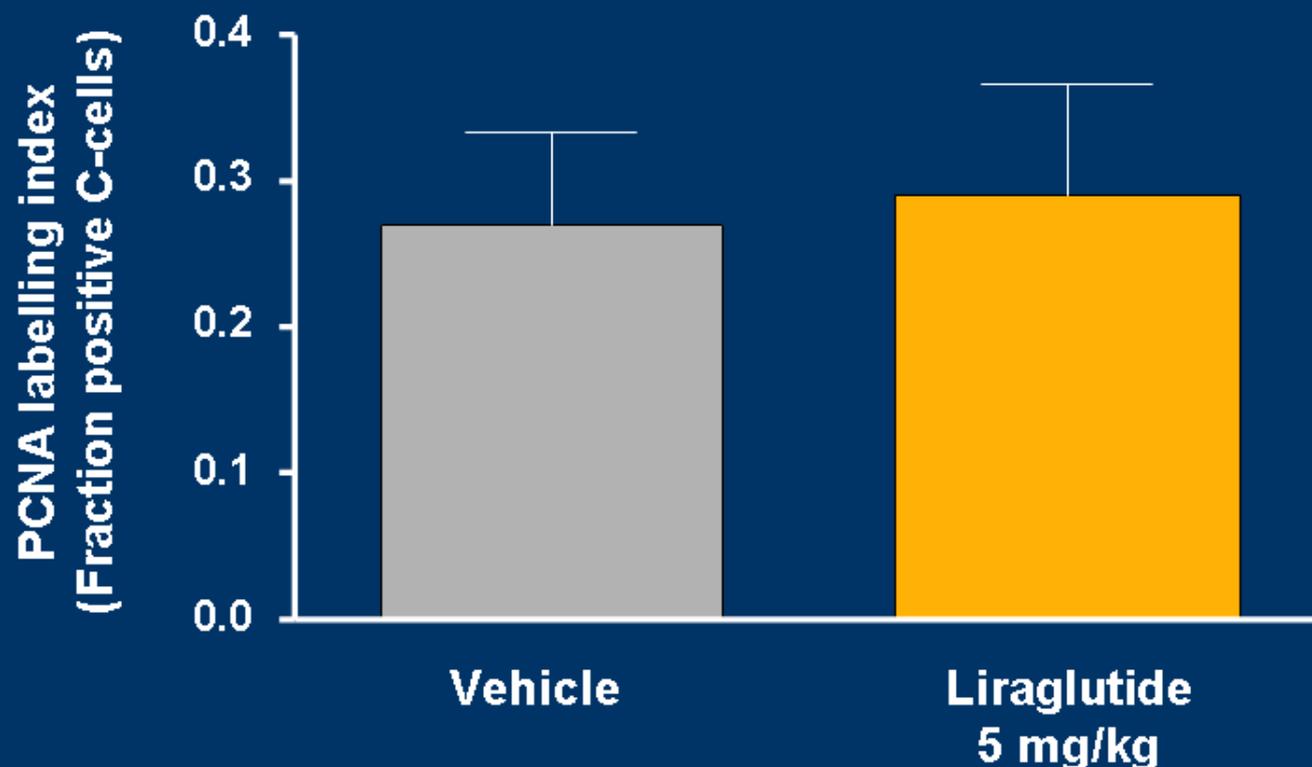
- Early calcitonin release in both rats and mice
- Preceded C-cell proliferation
- Calcitonin response most pronounced in mouse

# No Calcitonin Release in Non-human Primates



Plasma calcitonin in cynomolgus monkeys (Geometric mean and 95% CI; N=10/group)

# No C-cell Proliferation in Non-human Primates – 52-Week Study



Thyroid from cynomolgus monkeys treated 52 weeks  
Mean and 95% CI; N=6-8/group  
PCNA: proliferating cell nuclear antigen

# No C-cell Hyperplasia in Non-human Primates – 87-Week Study

|                                       |            |            |            |
|---------------------------------------|------------|------------|------------|
| <b>Dose (mg/kg)</b>                   | <b>0</b>   | <b>0.2</b> | <b>5.0</b> |
| <b>Fold human exposure</b>            | <b>N/A</b> | <b>8</b>   | <b>64</b>  |
| <b>C-cell hyperplasia (incidence)</b> | <b>0</b>   | <b>0</b>   | <b>0</b>   |

Thyroid from cynomolgus monkeys treated 87 weeks  
(n=10/group)

# Non-human Primate as a Model for C-cell Effects

- Short-term exposure with calcium and vitamin D can induce C-cell proliferation in non-human primates
- Long-term exposure with liraglutide did not induce C-cell proliferation in non-human primates

## *In vivo* Species Differences in Time to Occurrence and Events

| <b>Species</b>                   | <b>Calcitonin release</b> | <b>C-cell hyperplasia</b> | <b>C-cell neoplasia</b> |
|----------------------------------|---------------------------|---------------------------|-------------------------|
| <b>Mouse (weeks)</b>             | <b>1</b>                  | <b>9</b>                  | <b>64</b>               |
| <b>Rat (weeks)</b>               | <b>2</b>                  | <b>40</b>                 | <b>47</b>               |
| <b>Non-human primate (weeks)</b> | <b>None (up to 87)</b>    | <b>None (up to 87)</b>    | <b>None (up to 87)</b>  |

# C-cell Effects are GLP-1 Receptor Mediated

- Liraglutide highly specific for the GLP-1 receptor
  - More than 75 different receptors tested
    - Including known C-cell receptors
    - Including known cell activation and growth-related receptors
- C-cell effects observed with liraglutide reproduced with other GLP-1 receptor agonists
  - *In vitro* and *in vivo*

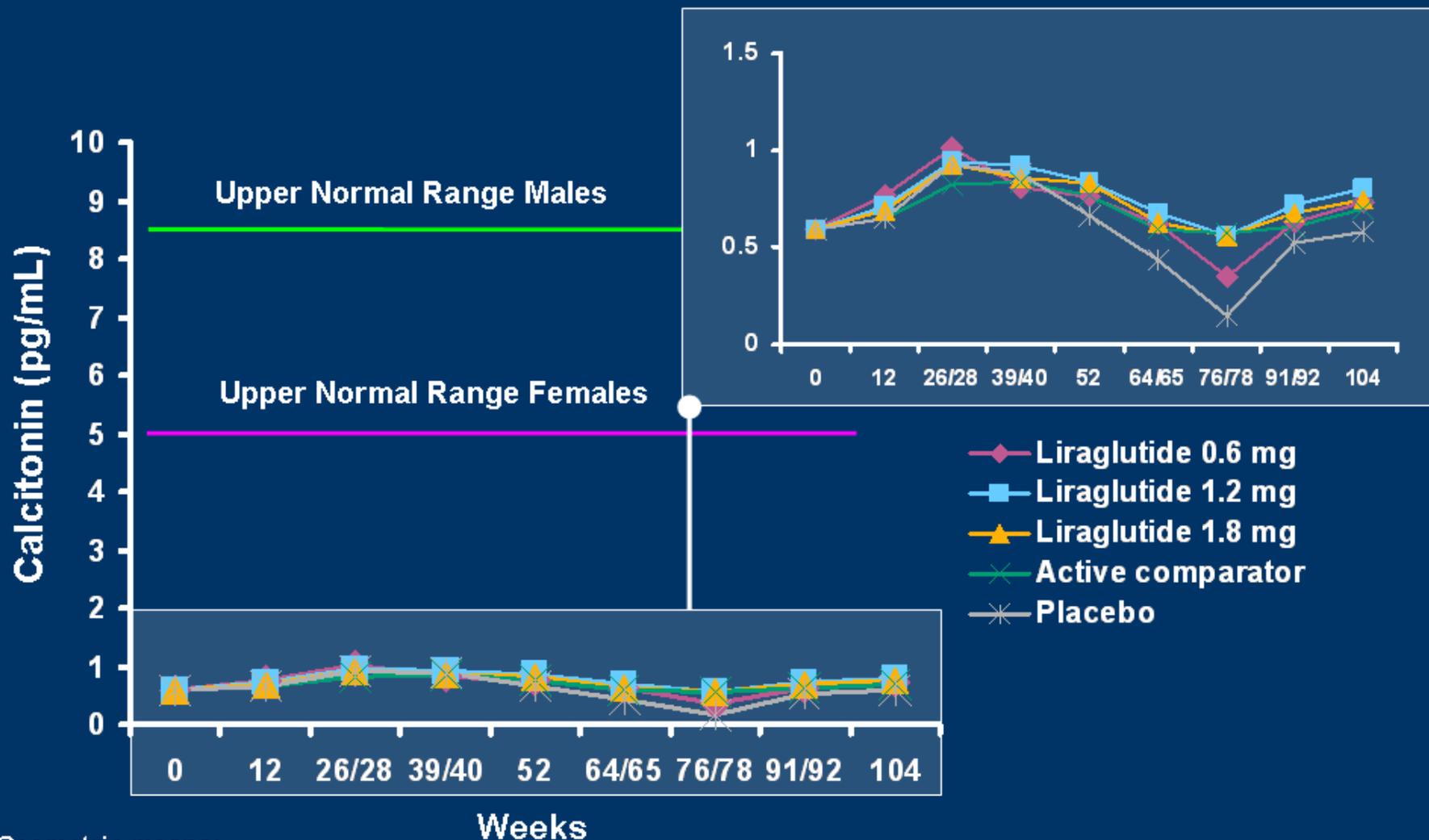
# Conclusion – Rodent C-cell Findings

- Rodent C-cell findings are GLP-1 receptor mediated
- Calcitonin is a sensitive marker for C-cell GLP-1 receptor activation
- No C-cell related findings in non-human primates
  - No calcitonin release
  - No C-cell proliferation
- Human relevance must be assessed in context of the clinical data

# Calcitonin Assessments in Humans

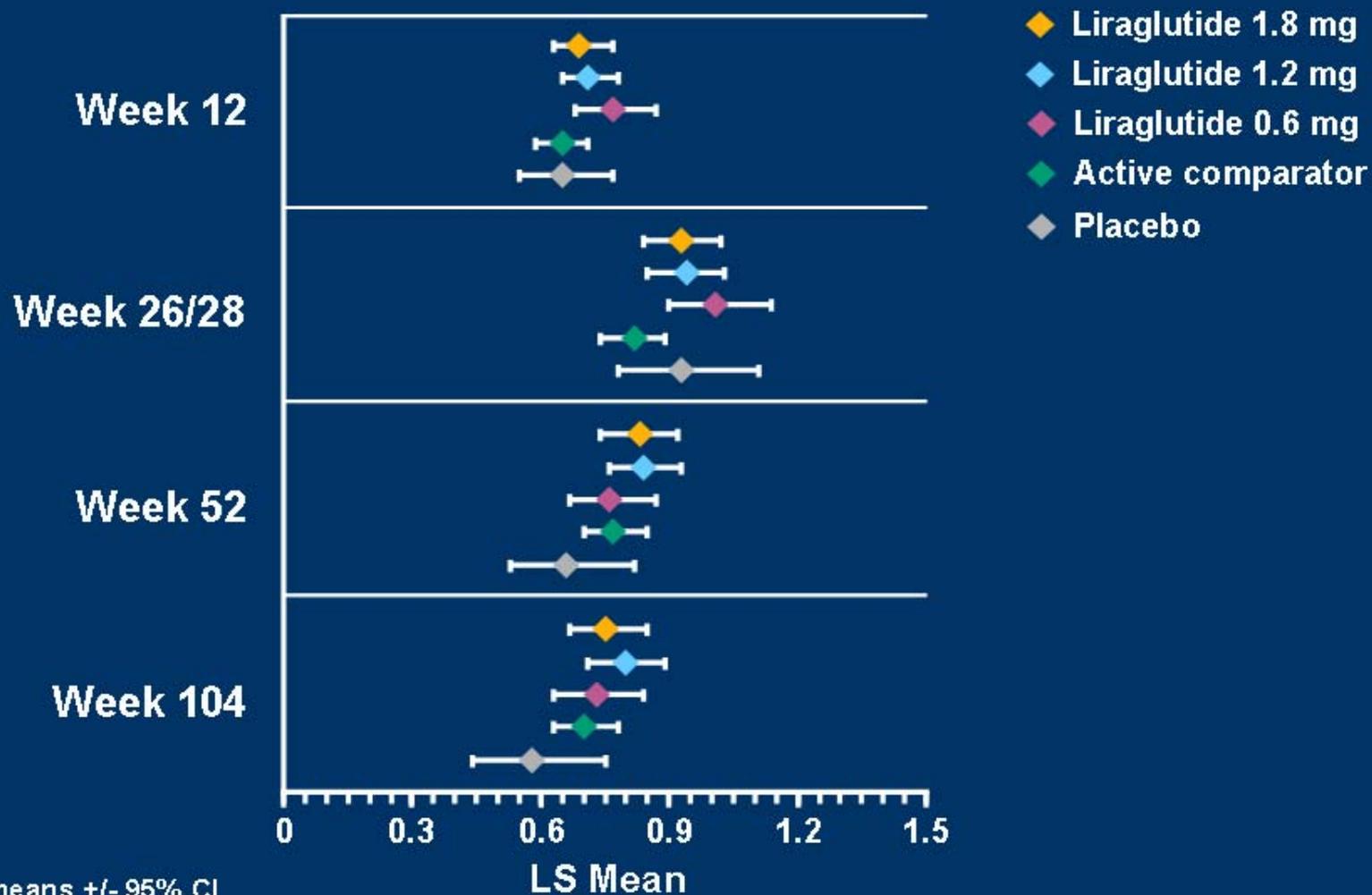
- Unstimulated calcitonin in >5,000 subjects
- Central tendencies and outliers analyzed
- Calcium stimulation test
  - Powered to detect 50% difference in stimulated plasma calcitonin levels

# Unstimulated Calcitonin Levels (24 months)



Geometric means;  
Study 1572 and 1573

# Unstimulated Calcitonin Levels (24 months)



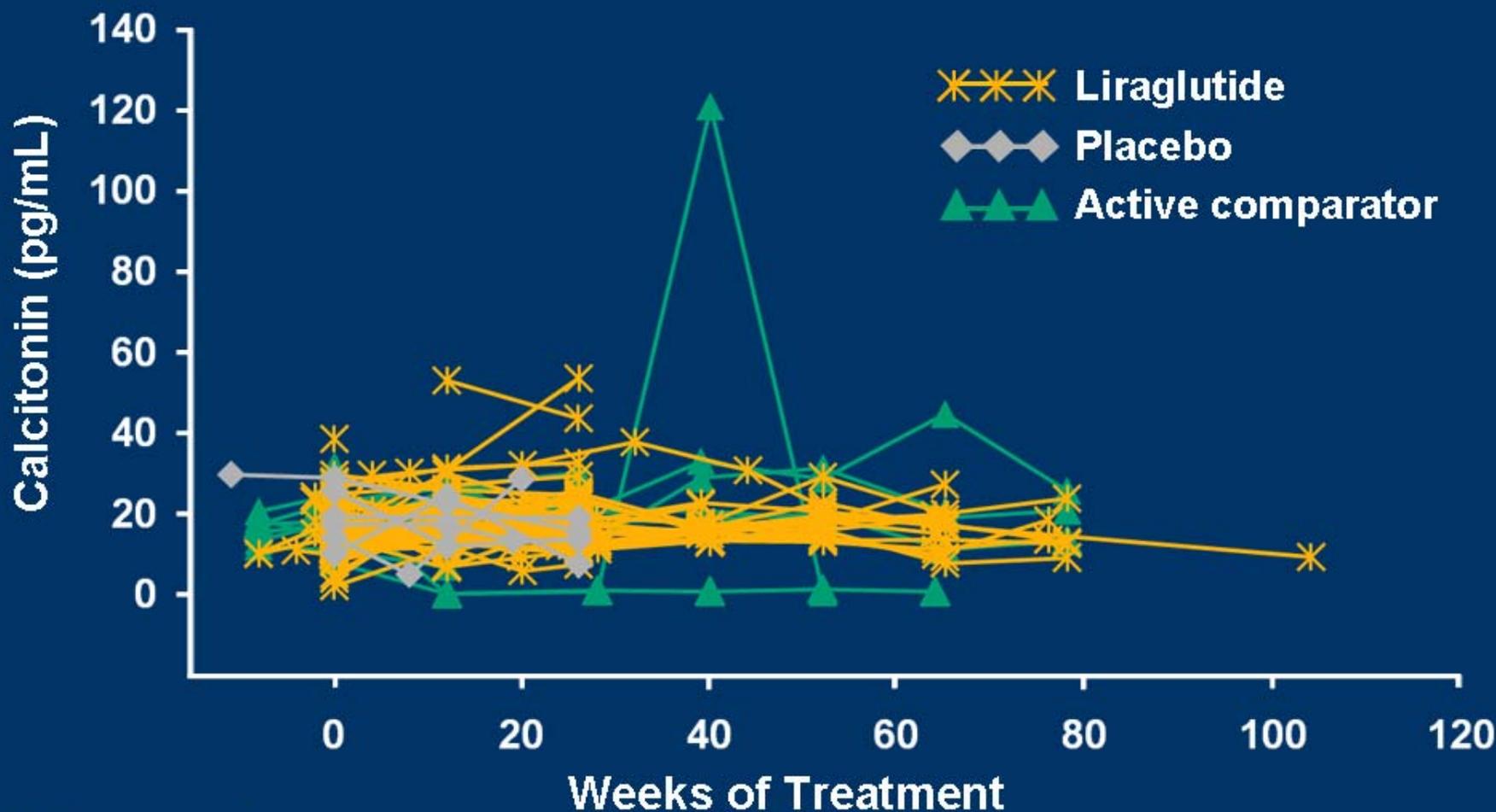
Geometric means +/- 95% CI  
Study 1572 and 1573

# Percentage of Subjects with Calcitonin Shifting $\geq$ UNR

| <b>Week</b>  | <b>Liraglutide</b> | <b>Placebo</b> | <b>Active comparator</b> |
|--------------|--------------------|----------------|--------------------------|
| <b>20-28</b> | <b>2.2%</b>        | <b>1.7%</b>    | <b>1.8%</b>              |
| <b>48-52</b> | <b>1.9%</b>        | <b>1.6%</b>    | <b>2.0%</b>              |
| <b>76-78</b> | <b>2.3%</b>        | <b>1.6%</b>    | <b>3.4%</b>              |

UNR: upper normal range

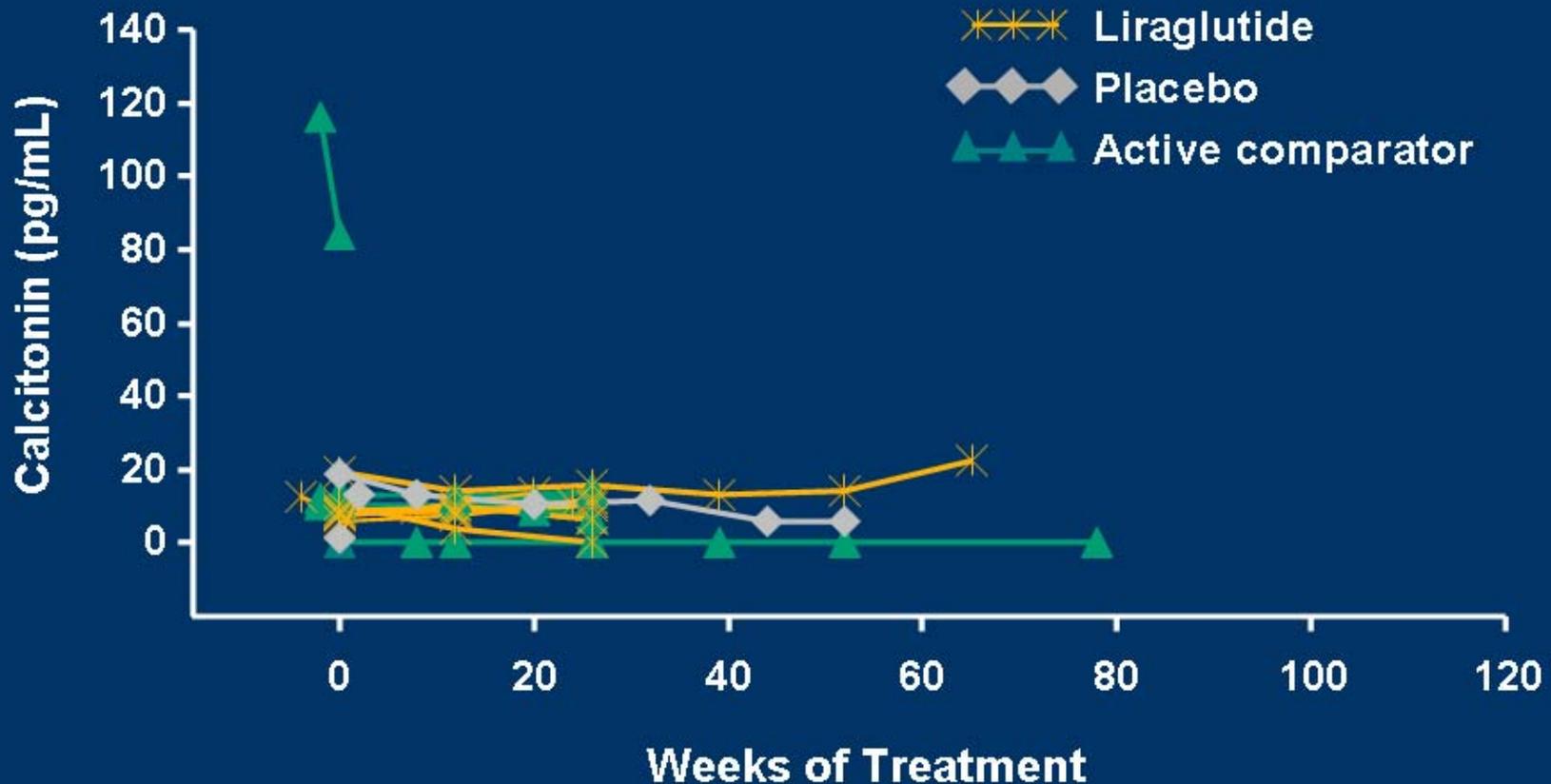
# Male Subjects with Calcitonin Values $\geq 2x$ UNR



UNR: upper normal range

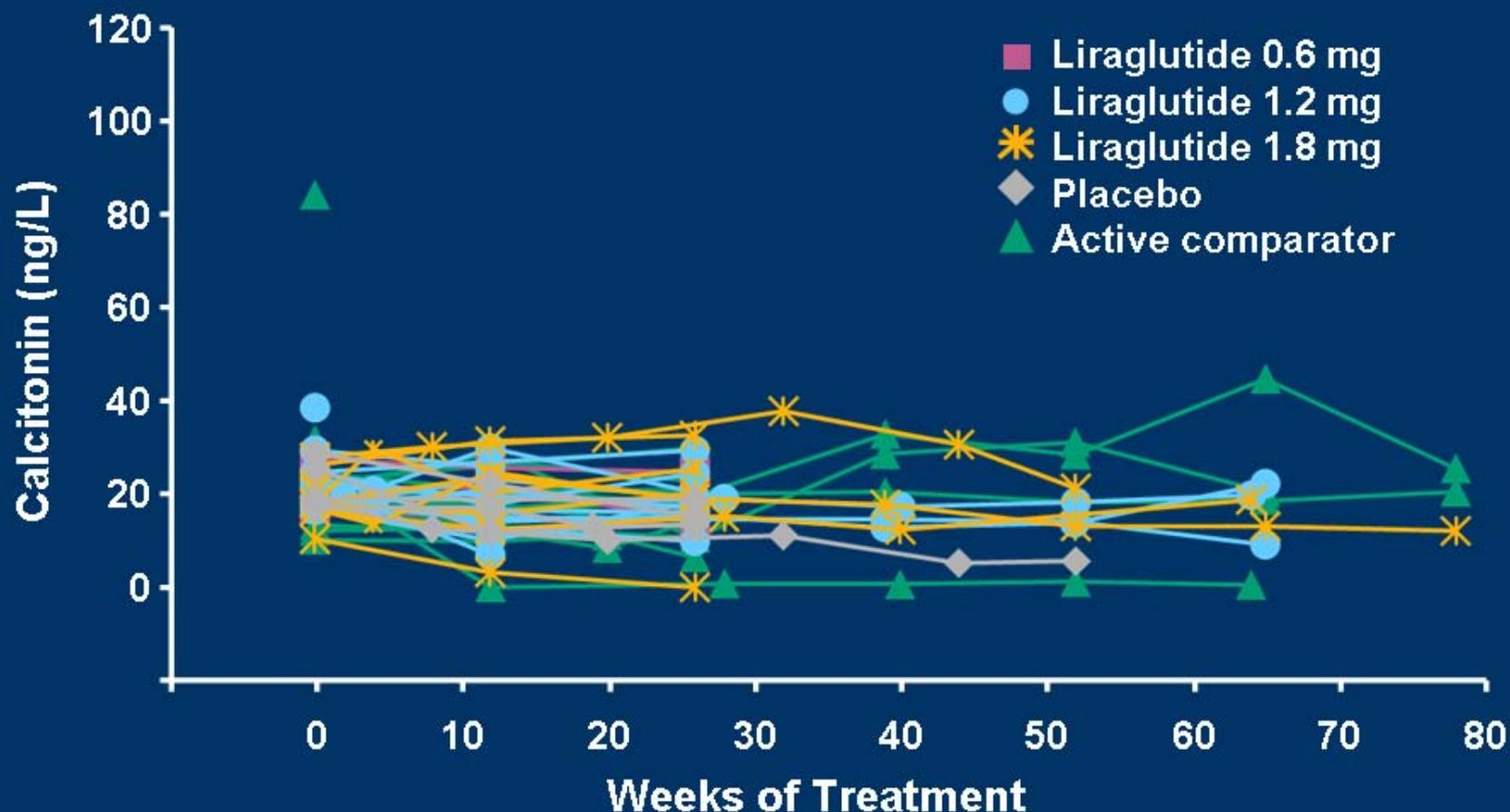
Male subject 1697/xx0001 (active comparator) with high calcitonin at Week 0 (1725 ng/L) and Week 12 (1083 ng/L) is not shown

# Female Subjects with Calcitonin Values $\geq 2x$ UNR



UNR: upper normal range

# Subjects with Baseline Calcitonin $\geq 2$ UNR

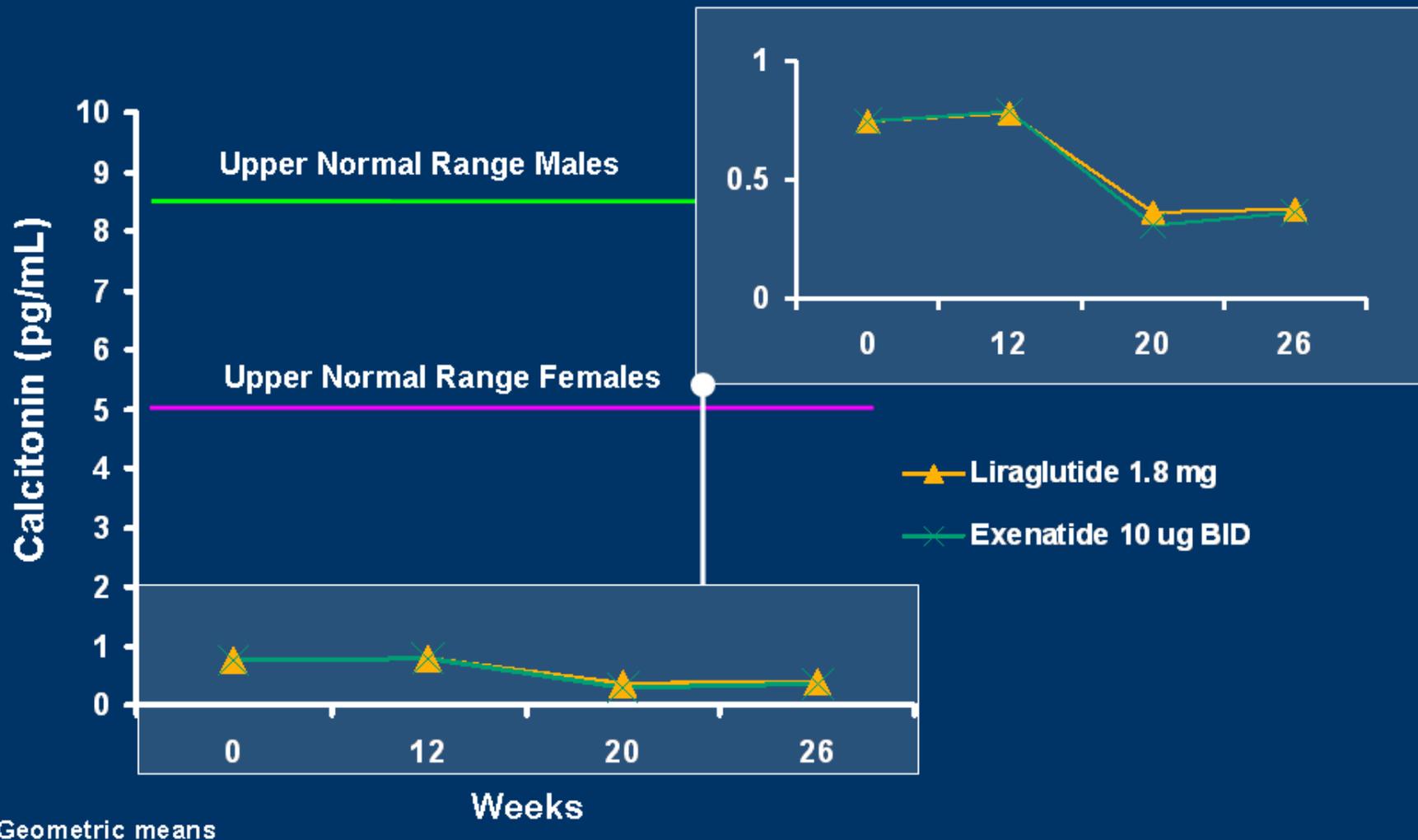


Subjects in trials 1436, 1572, 1573, 1574, 1697, 1797 and 1807

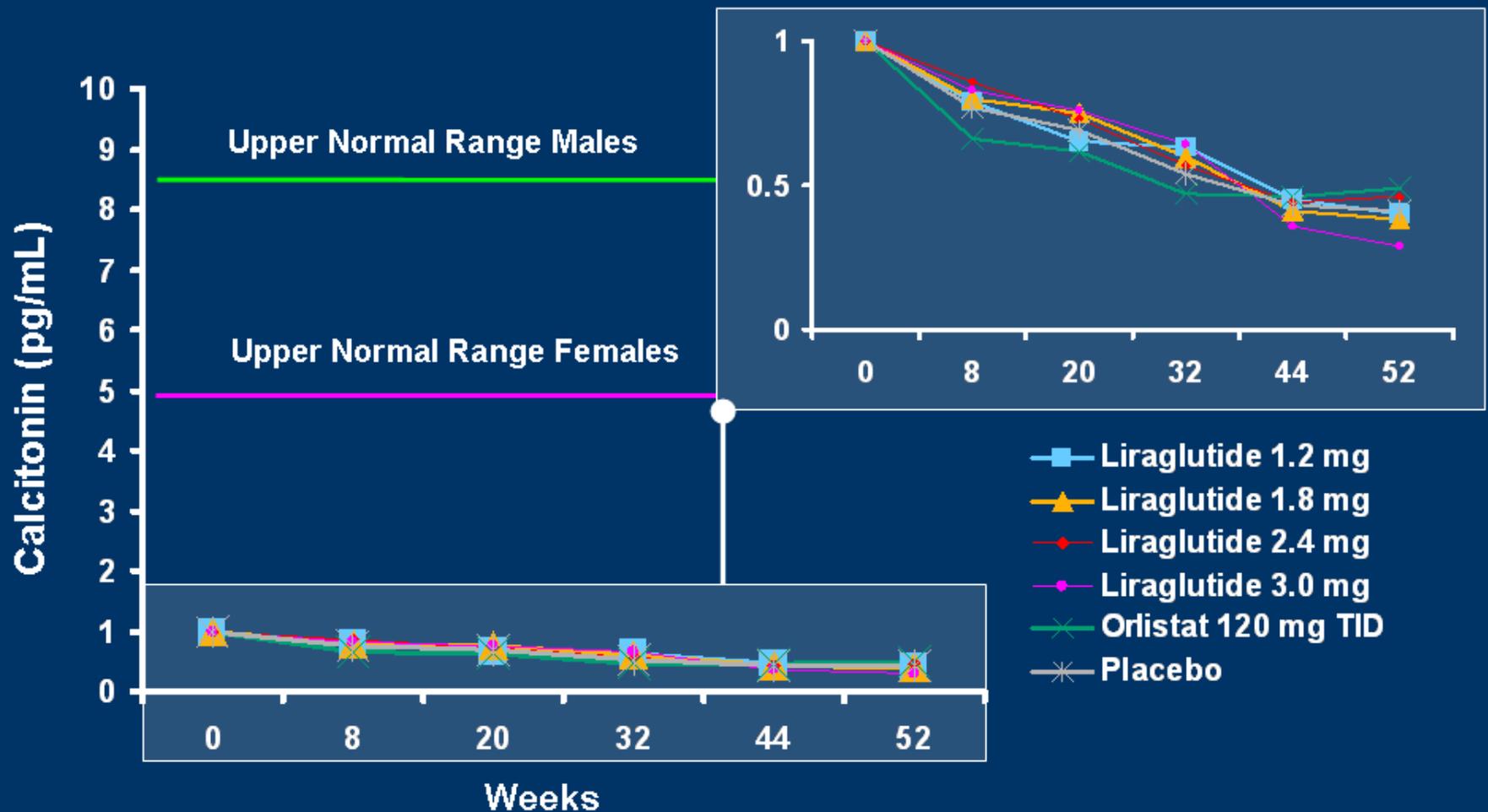
Upper normal range (UNR) for calcitonin: 8.4 ng/L for males and 5.0 ng/L for females

High calcitonin levels for subject xx0001 not shown (1725 ng/L at baseline and 1083 ng/L at week 12)

# Unstimulated Calcitonin Levels – Liraglutide / Exenatide Study (26 weeks)

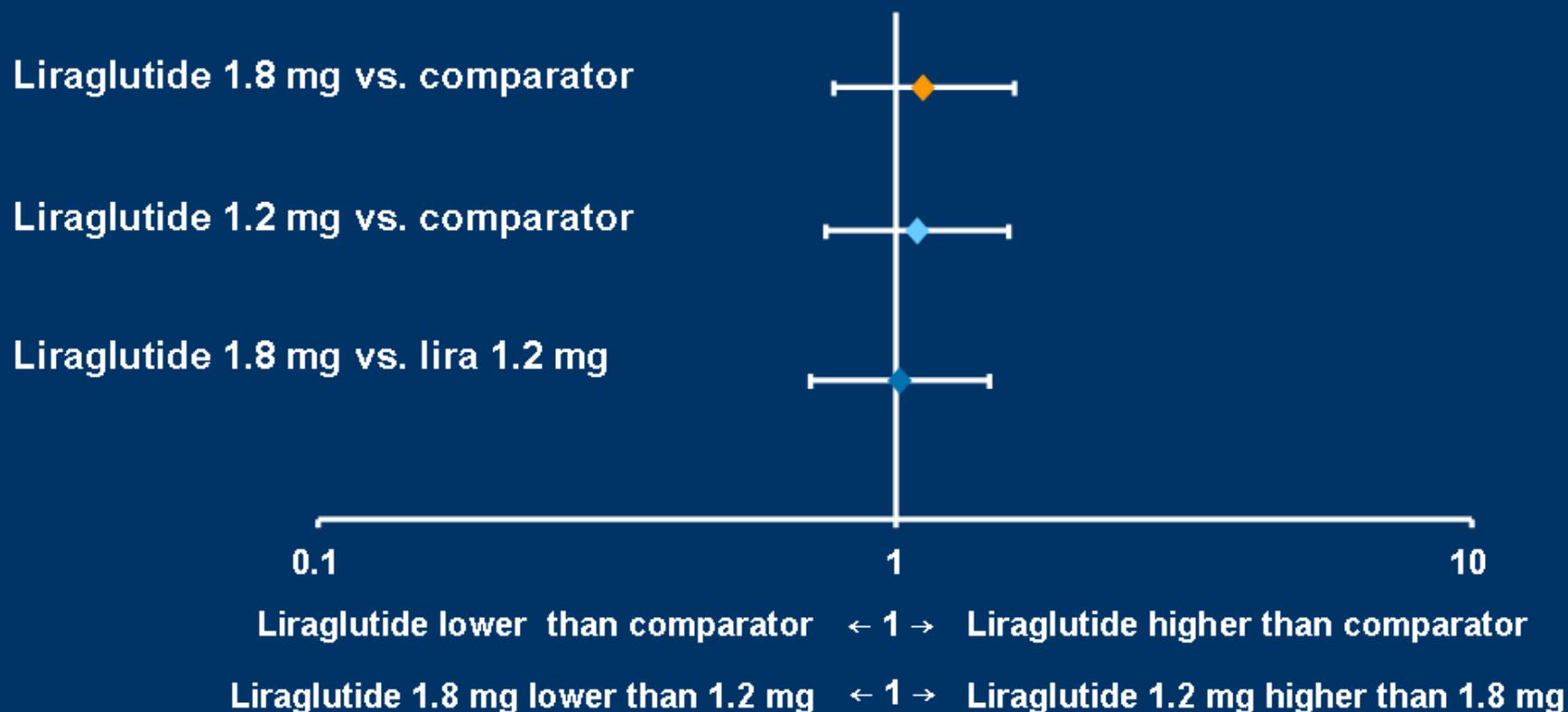


# Unstimulated Calcitonin Levels – Non-Diabetic Obese Subjects (52 weeks)



Geometric means

# Calcium Stimulation Test – Peak to Basal Ratio

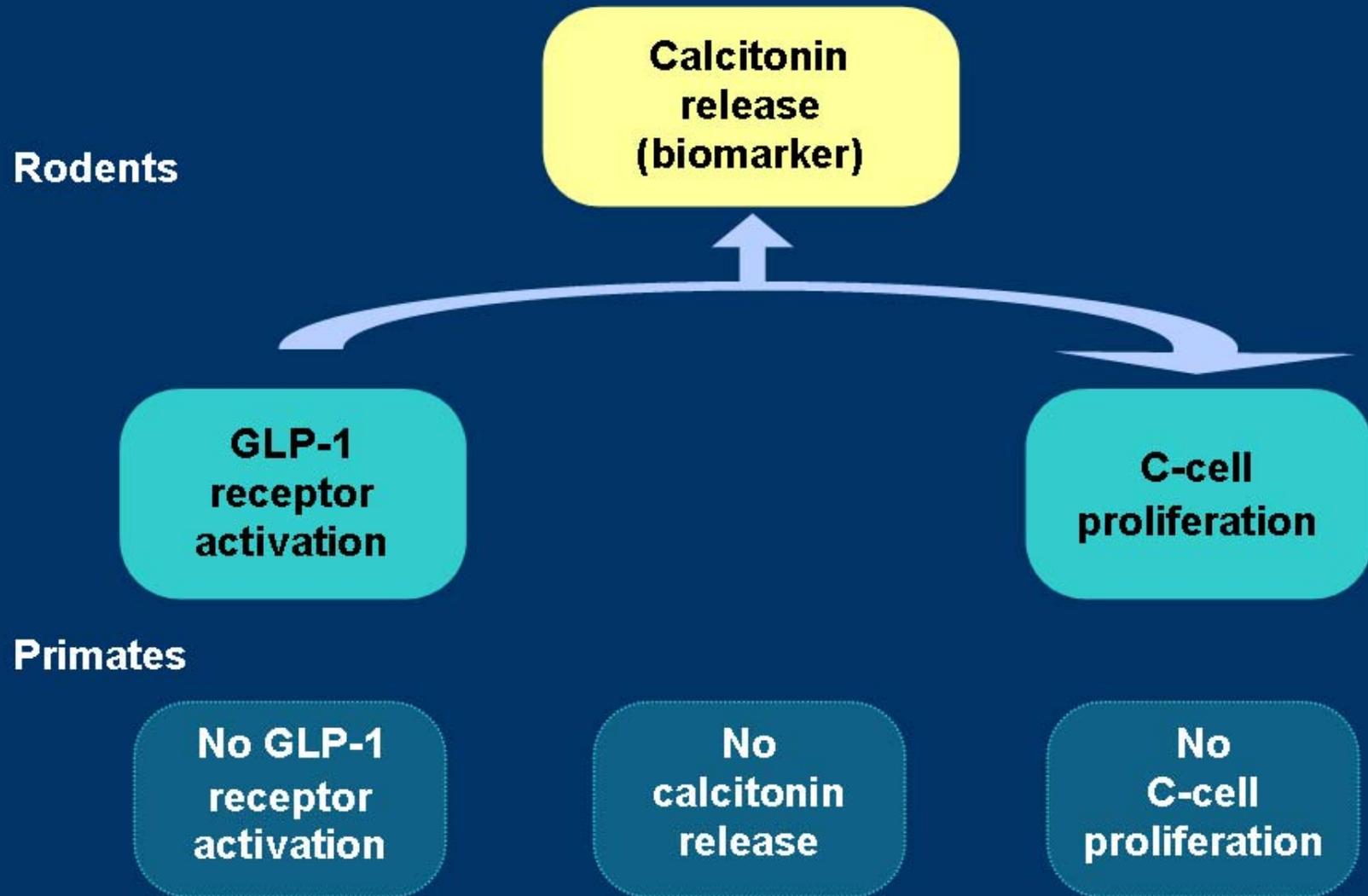


# Human C-cell Histopathology Findings

| Trial/<br>Subject<br>ID        | Gender | Reason for<br>Thyroidectomy  | Treatment   | Duration of<br>Treatment | Pathology  |
|--------------------------------|--------|--|---|--------------------------|--|
| 1697/<br>xx0001 <sup>(a)</sup> | Male   | Elevated calcitonin (1023 ng/L)<br>two months pre-randomization                              | Glimepiride+<br>metformin+<br>insulin<br>glargine | 145 days                 | Medullary thyroid<br>carcinoma/<br>blood calcitonin increased/<br>benign thyroid nodules           |
| 1572/<br>xx4012                | Male   | Elevated calcitonin three months<br>post-randomization (12.1 ng/L)                           | Glimepiride+<br>metformin                         | 370 days                 | Neoplastic C-cell<br>hyperplasia (medullary<br>carcinoma <i>in situ</i> )                          |
| 1573/<br>xx5008                | Male   | Elevated calcitonin at baseline<br>(22.3 ng/L)   | Liraglutide<br>1.8 mg                             | 28 days                  | Bilateral neoplastic nodular<br>C-cell hyperplasia   |
| 1572/<br>xx8002 <sup>(a)</sup> | Male   | Elevated calcitonin (21.5 ng/L) at<br>randomization  | Liraglutide<br>0.6 mg                             | 190 days                 | Bilateral nodular goiter,<br>C-cell hyperplasia  |
| 1572/<br>xx1008 <sup>(a)</sup> | Male   | Elevated calcitonin (22.3 ng/L)<br>nine months post-randomization<br>(15.1 ng/L at baseline) | Liraglutide<br>1.8 mg                             | 363 days                 | Papillary microcarcinoma/<br>physiological C-cell<br>hyperplasia/ goiter/benign<br>thyroid nodules |
| 1573/<br>xx1006                | Female | Elevated stimulation test at 12<br>months (peak calcitonin 94 ng/L)                          | Liraglutide<br>1.2 mg                             | 484 days                 | Diffuse C-cell hyperplasia   |

<sup>a</sup>Reported after the 120-day safety update. Reference range: 0.7–8.4 ng/L. Calcium Stimulation Test (CST), upper normal range 90 ng/L for female and 130 ng/L for male subjects.

# C-cell Findings are a Rodent Phenomenon



# Presentation Overview

- Background on phase 3 program
- Efficacy
  - Glycemic control
    - Hypoglycemia
  - Body weight
- Safety
  - Thyroid adverse events

# Papillary Carcinoma and Baseline Thyroid Abnormalities

|   | Liraglutide | Non-liraglutide |
|---|-------------|-----------------|
| Papillary carcinoma N (R)                                   | 5 (1.6)     | 1 (0.6)         |
| Fraction with abnormal ultrasound or calcitonin at baseline | 4/5         | 1/1             |
| Fraction with microcarcinoma (<1 cm)                        | 4/5         | 1/1             |

N = Number of subjects; R = Events/1000 subject years of exposure

# Goiter and Baseline Thyroid Abnormalities

|  | Liraglutide     | Non-liraglutide |
|--|-----------------|-----------------|
| <b>Goiter N (R)</b>  | <b>17 (5.8)</b> | <b>4 (2.5)</b>  |
| <b>Fraction with abnormal calcitonin at baseline or history of thyroid disease</b> | <b>11/17</b>    | <b>3/4</b>      |

N = Number of subjects; R = Events/1000 subject years of exposure

# Clinical Perspectives on the Thyroid and Calcitonin

Dr. Gilbert Daniels

Co-Director, Thyroid Clinic

Massachusetts General Hospital

Professor of Medicine, Harvard Medical School

# A Clinical Perspective

- Is there evidence that liraglutide stimulates human C-cells?
- Is there any significance of thyroid papillary carcinoma in the liraglutide program?
- What are the implications of screening for thyroid follicular and/or C-cell disorders?

# C-cell Hyperplasia

- Up to 33% of unselected thyroids
- In the absence of hereditary medullary thyroid carcinomas (MTC) – no evidence that C-cell hyperplasia is precursor of MTC
- No benefit in finding C-cell hyperplasia in general population

# Calcitonin Screening in Individuals with Abnormal Thyroids

- 22,824 individuals (most with thyroid nodules) screened using calcitonin measurements
- 114 (0.5%) medullary thyroid carcinomas discovered

Pacini et al 1994

Hahm et al 2001

Vierhapper et al 1997

Karanikas et al 2004

Niccoli et al 1997

Elisei et al 2004

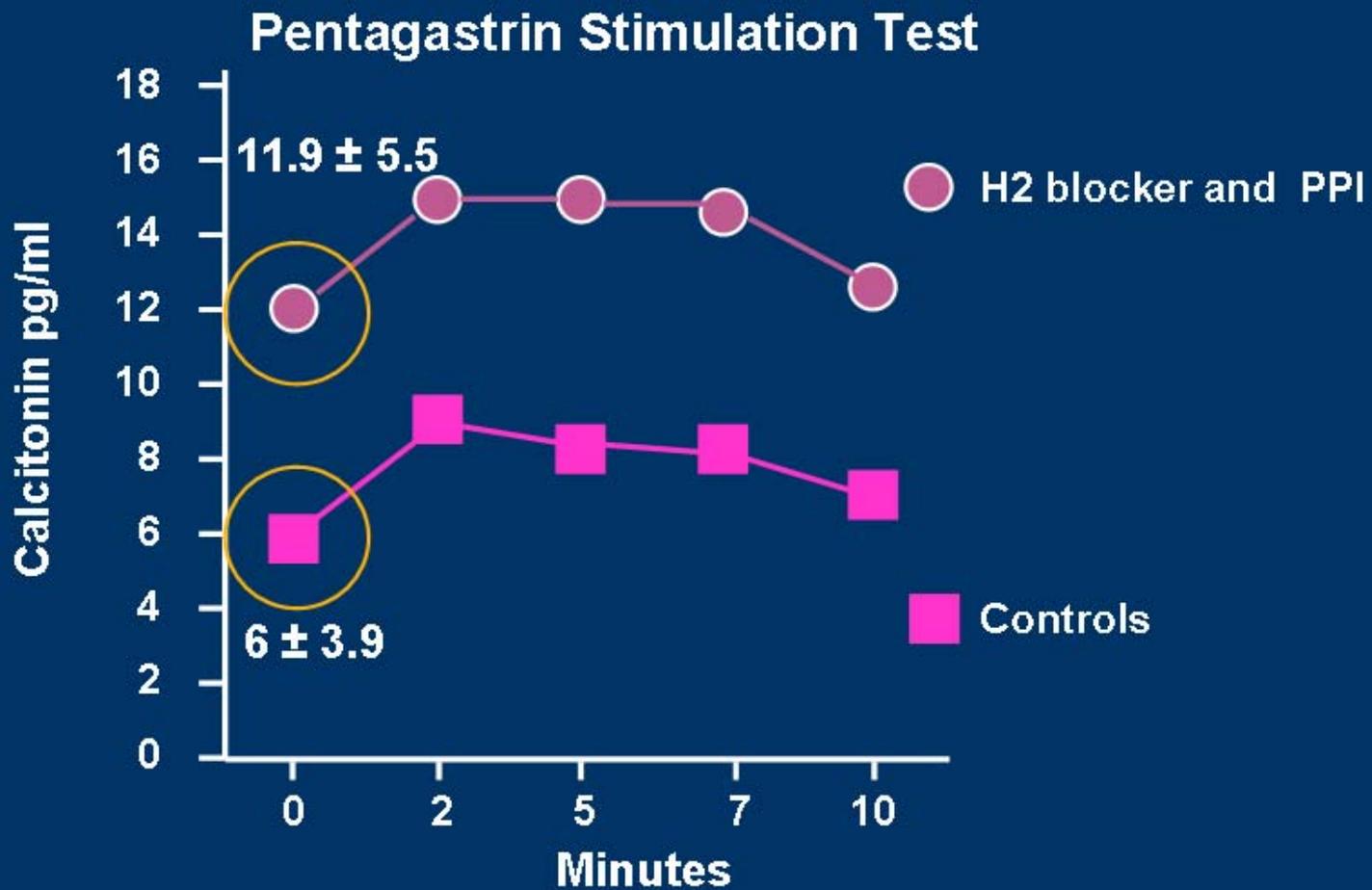
Kaserer et al 1998

Costante et al 2007

# Calcitonin Screening

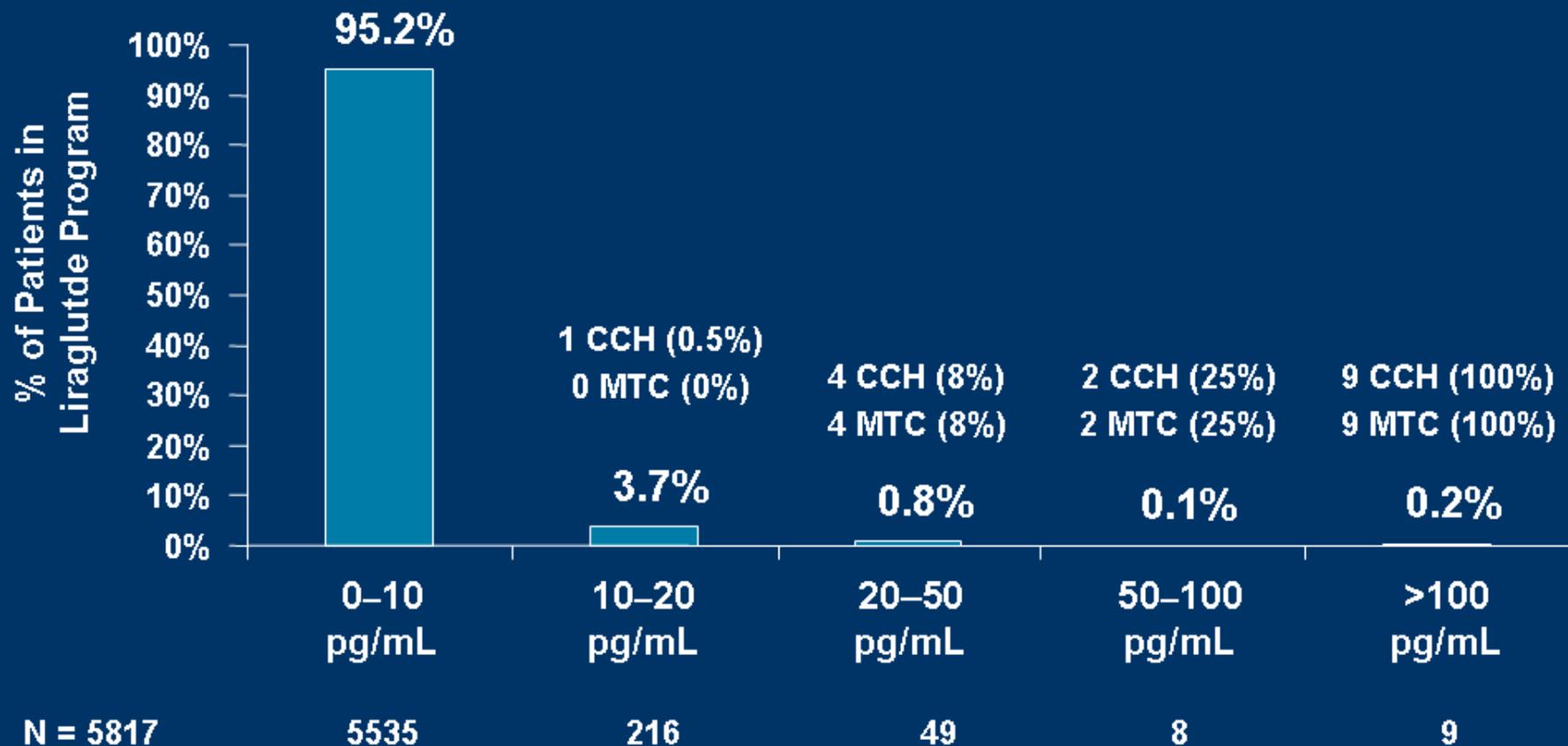
- American Thyroid Association does not recommend routine calcitonin screening
  - Even in patients with thyroid nodules
- Only substantial calcitonin levels are accurate predictors of clinically significant C-cell disease
- No merit in a calcitonin screening program

# Impact of H2 Blockers and Proton Pump Inhibitors on Calcitonin Measurements



Erdogan MF, Gursoy A, Kulaksizoglu, *J Endocrinol Invest* 29:771, 2006.

# Outcomes of Calcitonin Screening in Individuals with Underlying Thyroid Nodules



Constante G et al. *J Clin Endocrinol Metab* 92:450-455, 2007.

# Is There Any Clinical Relevance to the Rodent C-cell Findings for Humans?

- Marked difference in C-cell neoplasia incidence between rats and humans
- Calcitonin is THE marker of C-cell activation
- GLP-1 agonists stimulate rodent C-cells but do not stimulate C-cells in nonhuman primates
- GLP-1 agonists do not activate C-cells in humans as evidence by a lack stimulation of calcitonin secretion
  - No increase in mean calcitonin levels over time (up to 2 years)
  - No increase in calcitonin levels in people with elevated baseline calcitonin

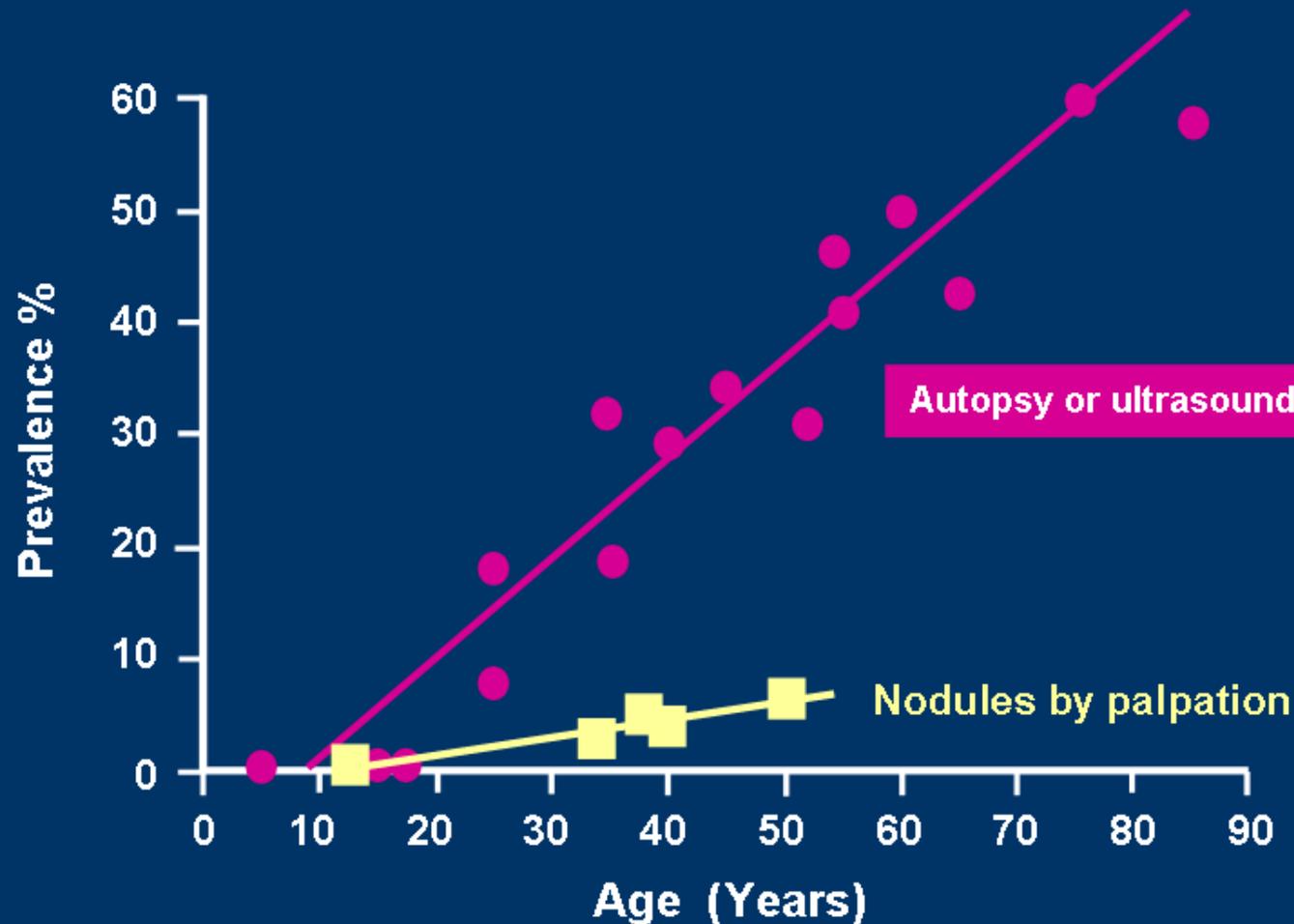
# C-cell Pathology in Development Program

- Six cases of C-cell pathology
  - Four cases of C-cell hyperplasia (one with nodular neoplastic C-cell hyperplasia) in liraglutide group, three of whom had elevated calcitonin prior to study drug administration
  - One medullary thyroid carcinoma and one MTC *in situ* in non-liraglutide treated subjects
- Four subjects on liraglutide with C-cell hyperplasia diagnosed by histology had no consistent change in calcitonin levels in response to liraglutide administration

# Thyroid Follicular Cells

- Distinct from C-cell in origin, abundance, function
- Give rise to goiters, nodules, and most thyroid cancers
- No evidence for disorders of follicular cells in any animal model including humans

# Thyroid Nodules Are Common



Mazzaferri E. *NEJM* 1993; 328: 553.

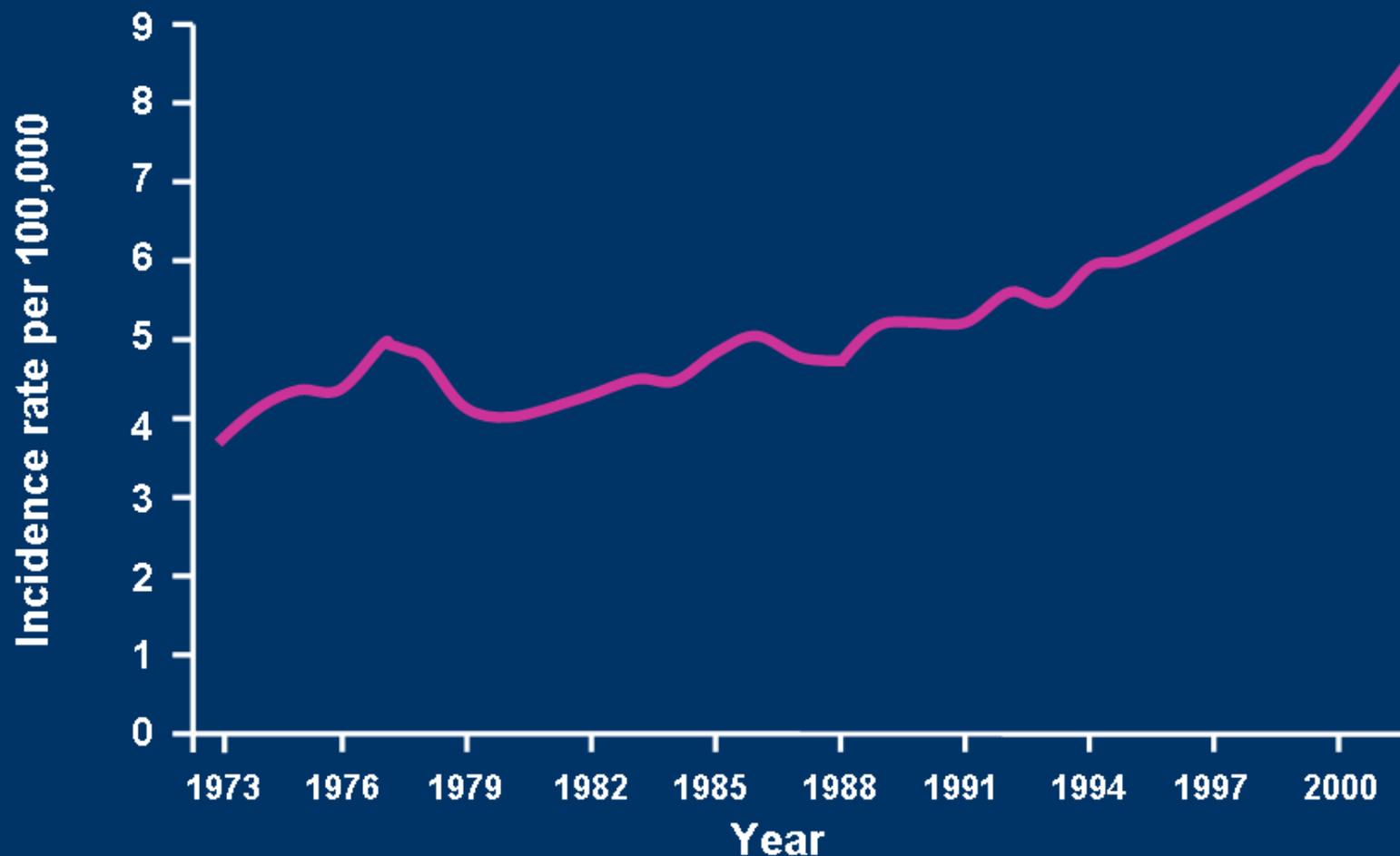
# Thyroid Nodules

- 20-50% have thyroid nodules  $>1$  cm upon ultrasound
  - Of those, 25% would require surgery
  - 10% of total with nodules would have overt papillary thyroid cancer
- Many with nodules not having thyroid surgery would be unnecessarily frightened

# Papillary Thyroid Microcarcinomas (<1 centimeter)

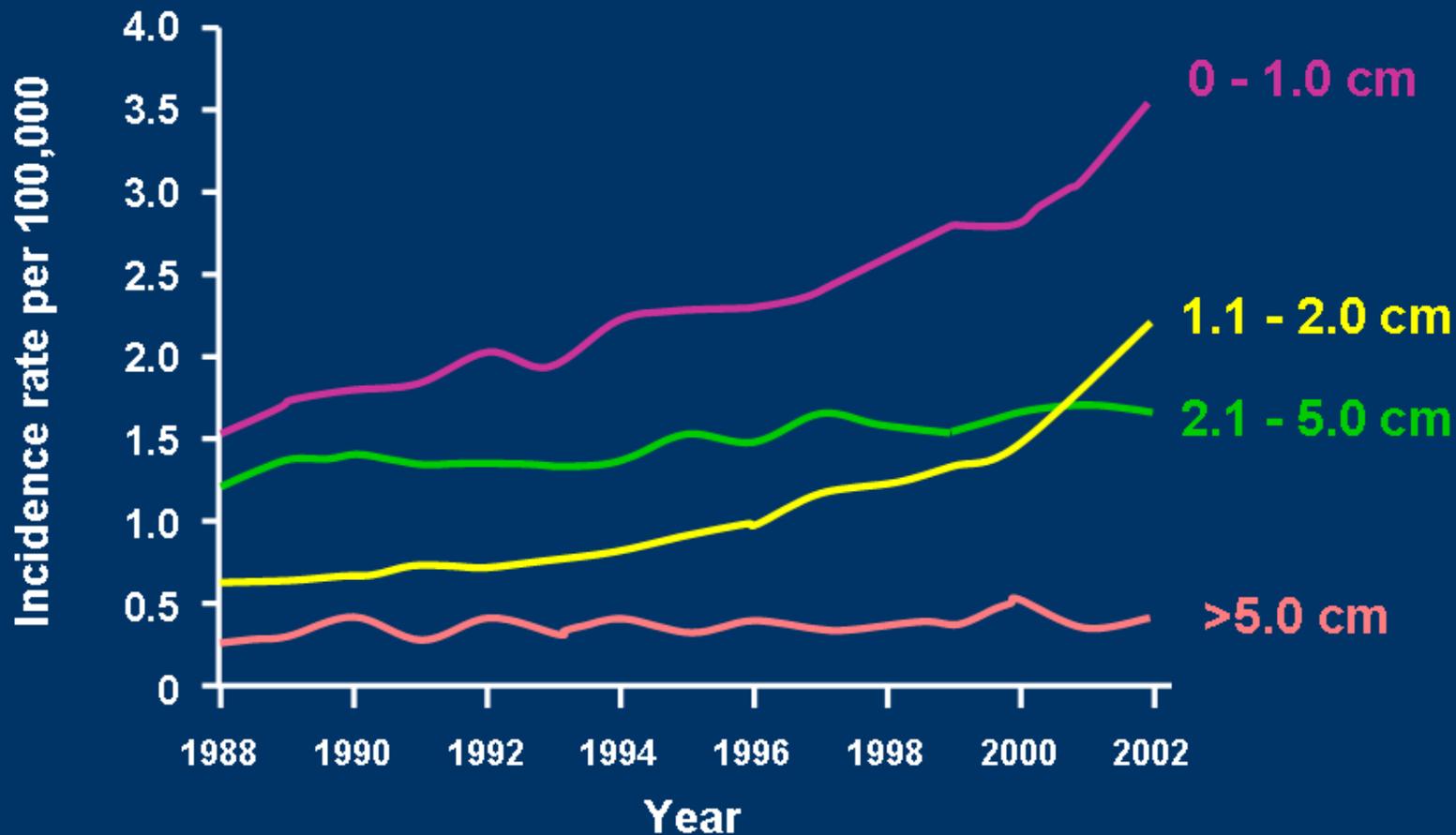
- Occur in up to 10–30%
- Typically incidental finding
- Generally of no clinical consequence
- 98% are never discovered
- No major thyroid organization recommends screening

# Thyroid Cancer Incidence 1973 – 2002



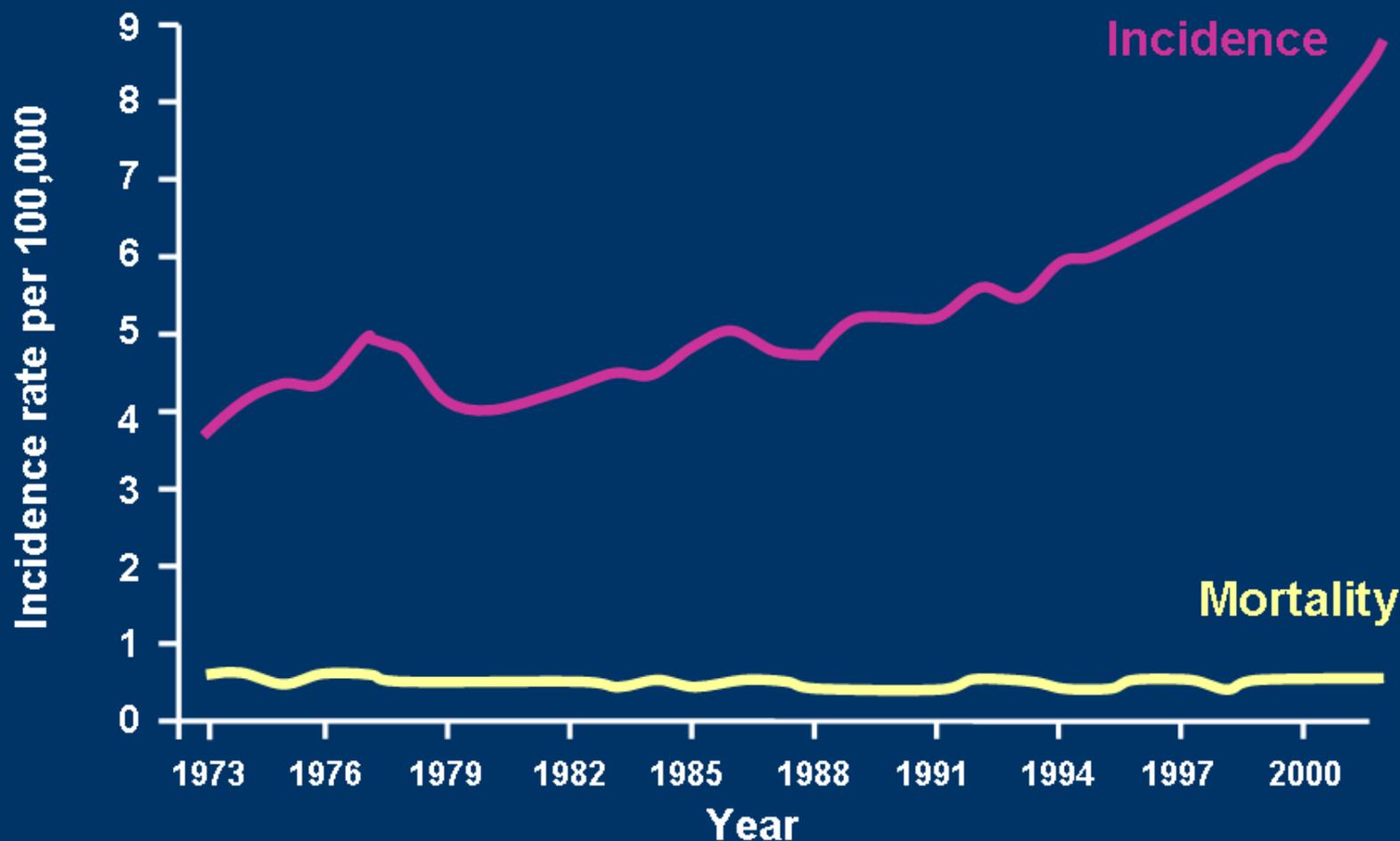
Davies et al, *JAMA* 2006; 195: 2164.

# Papillary Thyroid Carcinoma Size 1988 – 2002



Davies et al, *JAMA* 2006; 195: 2164.

# Thyroid Cancer Incidence and Mortality 1973 – 2002



Davies et al, *JAMA* 2006; 195: 2164.

# Liraglutide versus Causality for Papillary Thyroid Carcinoma

- Five cases of papillary thyroid carcinomas <1.5 cm
  - All cases incidentally identified by thyroid screening procedures
    - 4 of 5 cases on liraglutide identified based on elevated calcitonin levels (3 at baseline)
    - One case identified by screening ultrasound
- Screening program led to diagnosis
- No evidence liraglutide caused small papillary carcinomas

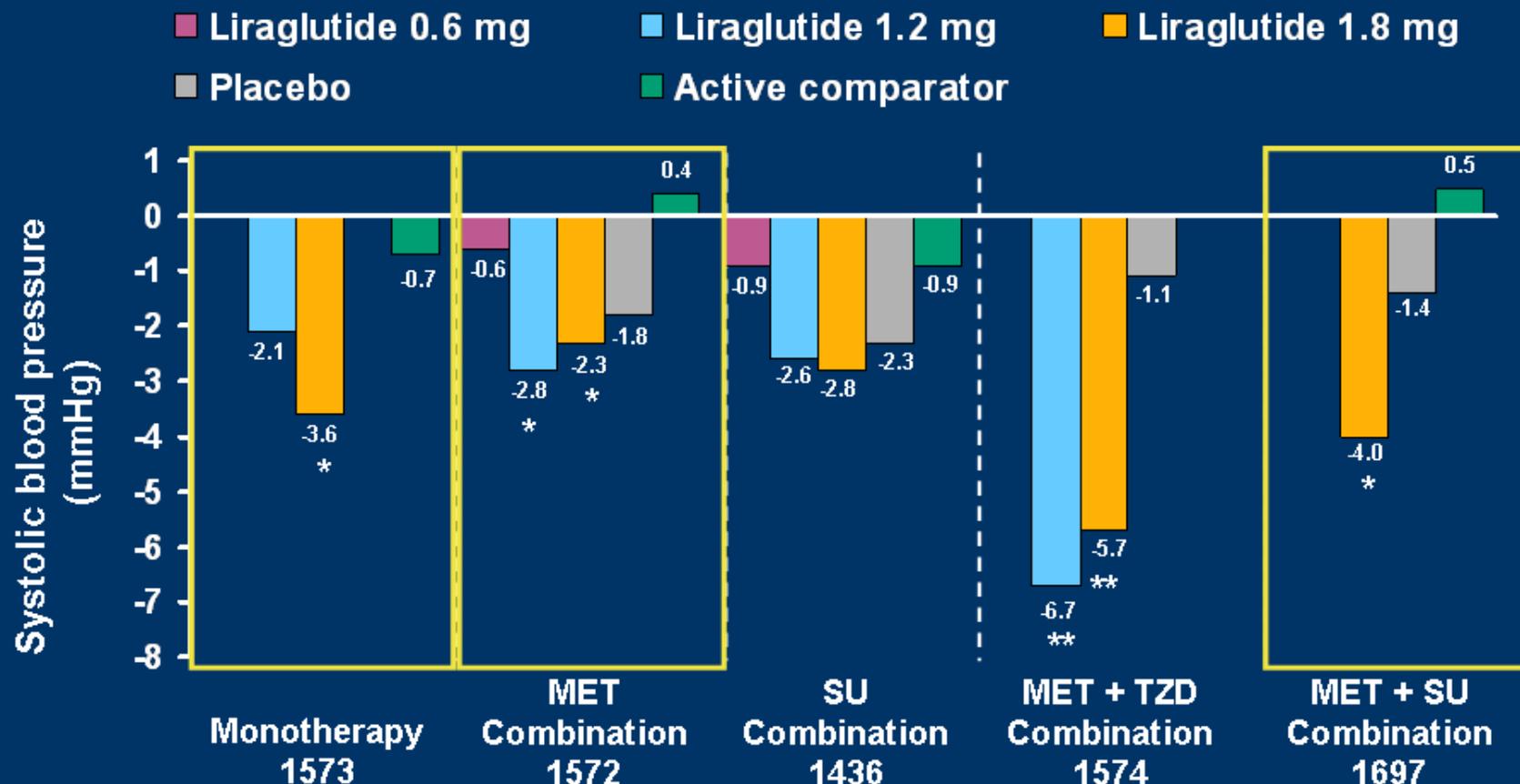
# Thyroid Follicular and C-cell Conclusions

- No evidence for relevance of rodent C-cell findings for humans
- Papillary carcinomas incidental diagnosis based on screening procedures
- Screening for thyroid follicular and C-cell disease not warranted nor recommended

# Presentation Overview

- Background on phase 3 program
- Efficacy
  - Glycemic control
    - Hypoglycemia
  - Body weight
- Safety
  - Cardiovascular biomarkers

# Systolic Blood Pressure – Change from Baseline



\*Liraglutide significantly different from active comparator

\*\*Liraglutide significantly lower than placebo

Estimated changes LOCF data set

# Blood Pressure, Heart Rate and Lipids

- No significant effect on diastolic blood pressure
- Increase in heart rate of 2–4 beats/min
- No consistent treatment effects on lipid parameters
  - TG, FFA, LDL-C, TC, HDL or ApoB

# Presentation Overview

- Background on phase 3 program
- Efficacy
  - Glycemic control
    - Hypoglycemia
  - Body weight
- Safety
  - Cardiovascular adverse events (MACE)

# Patients with Cardiovascular Risk Factors

|   | % (N)              |
|---|--------------------|
| <b>Total N</b>  | <b>6638</b>        |
| <b>Age <math>\geq</math> 65 years</b>                           | <b>19.9 (1332)</b> |
| <b>Diabetes duration <math>\geq</math> 10 years</b>             | <b>25.3 (1677)</b> |
| <b>Hypertension</b>   | <b>54.8 (3636)</b> |
| <b>Hyperlipidemia</b>   | <b>50.6 (3358)</b> |
| <b>Coronary, cerebrovascular or peripheral vascular disease</b> | <b>15.5 (1030)</b> |
| <b>Creatinine clearance* <math>&lt;</math>90 ml/min</b>         | <b>26.0 (1729)</b> |
| <b>Creatinine clearance* <math>&lt;</math>60 ml/min</b>         | <b>3.6 (238)</b>   |

\* Estimated based on Cockcroft-Gault formula

# MACE analysis

- Retrospective
- No pre-planned adjudication
- Data analysed using different
  - MACE definitions (including validation of MACE events)
  - Populations
  - Comparators
  - Statistical approaches
- Development program gives an extensive randomized exposure experience

# Definition of Adverse Events – MACE Analysis

- MACE
  - Cardiovascular death
  - Myocardial infarction
  - Central nervous system hemorrhages and cerebrovascular accidents
- Three sets of search criteria for AEs applied using the standardized coding system for adverse events (MedDRA)
- Within MedDRA standard defined lists of adverse events belonging to the same category used (SMQs)

MedDRA: Medical Dictionary for Regulatory Activities – coding system for adverse events

SMQ: Standard MedDRA Query - defined list of adverse events belonging to the same category

# Definition of Adverse Events – MACE Analysis

Cardiovascular death

**“Custom  
MACE”**

FDA list of adverse  
events

MedDRA defined list (Narrow)

**“SMQ  
Narrow”**

MedDRA defined list (Broad)

**“SMQ  
Broad”**

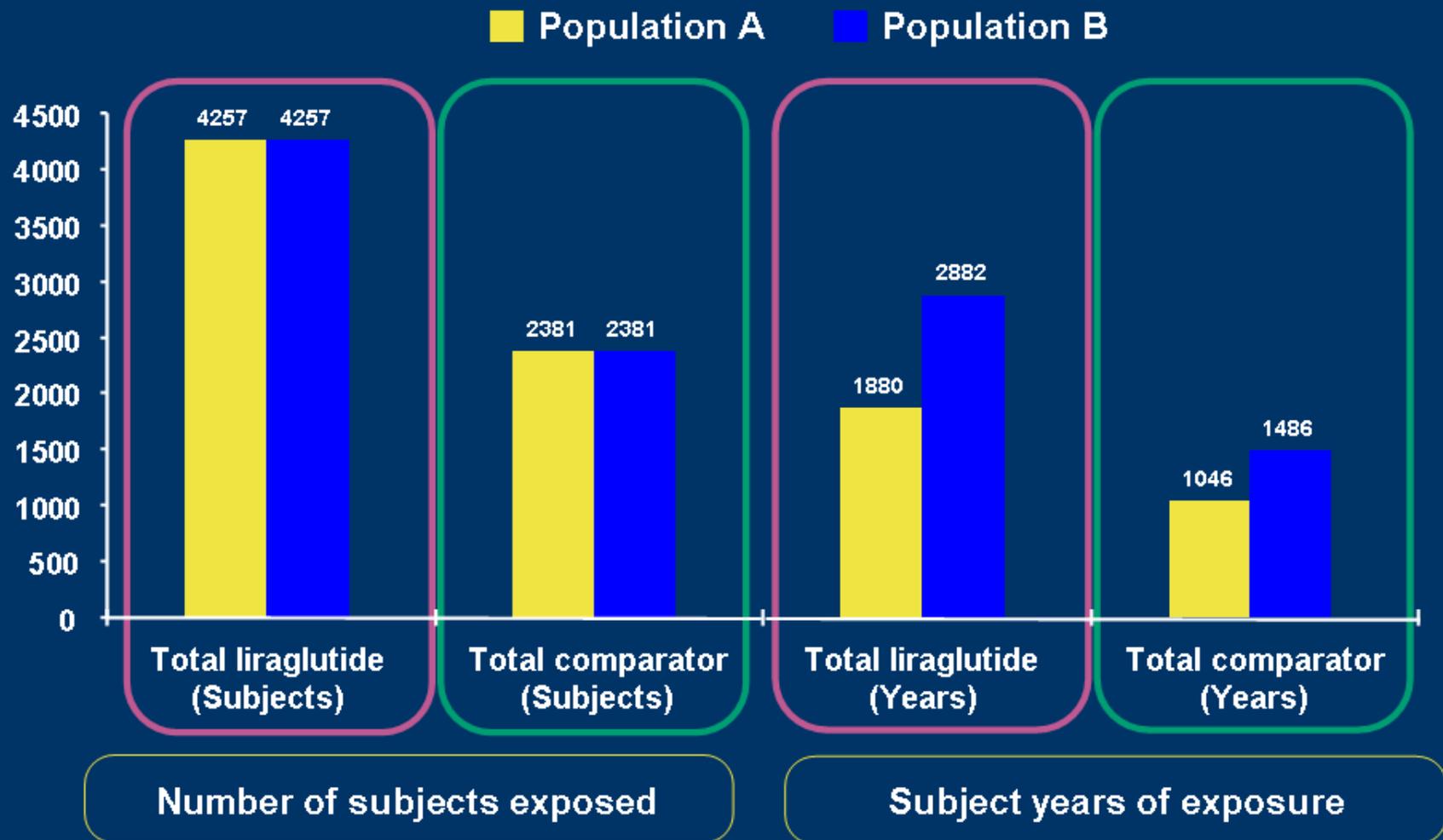
MedDRA: Medical Dictionary for Regulatory Activities – coding system for adverse events

SMQ: Standard MedDRA Query - defined list of adverse events belonging to the same category

# Population Definitions

- Two populations presented corresponding to the FDA briefing document
- Population A
  - Randomized and controlled phase 2 and 3 trials
  - Time up to measurement of primary endpoint
  - Same as population A2 in Novo Nordisk briefing book
- Population B
  - Population A plus people in open label controlled extensions of phase 2 and phase 3 studies
  - Same as population B in Novo Nordisk briefing book

# Exposure Across Populations – Number of Subject Exposed and Years of Exposure



# Number of Subjects Experiencing a MACE Event

|                       | Population A |           | Population B |           |
|-----------------------|--------------|-----------|--------------|-----------|
|                       | Liraglutide  | Control   | Liraglutide  | Control   |
| <b>Custom Total</b>   | <b>13</b>    | <b>13</b> | <b>21</b>    | <b>17</b> |
| <b>Custom Serious</b> | <b>11</b>    | <b>12</b> | <b>17</b>    | <b>15</b> |
| <b>Narrow Total</b>   | <b>22</b>    | <b>17</b> | <b>35</b>    | <b>24</b> |
| <b>Narrow Serious</b> | <b>15</b>    | <b>16</b> | <b>24</b>    | <b>19</b> |
| <b>Broad Total</b>    | <b>51</b>    | <b>35</b> | <b>69</b>    | <b>45</b> |
| <b>Broad Serious</b>  | <b>16</b>    | <b>16</b> | <b>25</b>    | <b>19</b> |

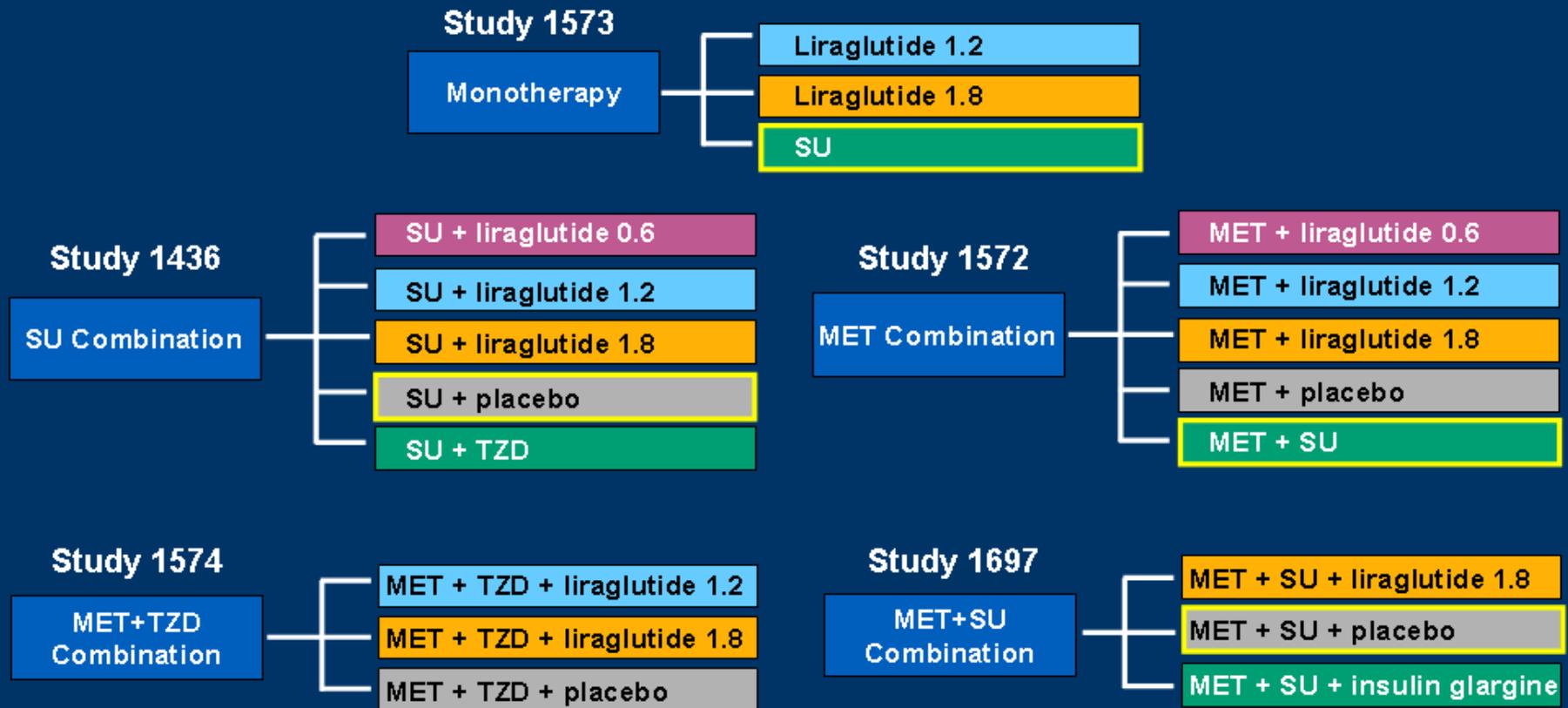
# MACE Incidence Rates – Overview

|                          |                | Population A |                  | Population B |                  |
|--------------------------|----------------|--------------|------------------|--------------|------------------|
|                          |                | Liraglutide  | Total comparator | Liraglutide  | Total comparator |
| <b>SMQ MACE (Broad)</b>  | <b>All</b>     | <b>2.71</b>  | <b>3.35</b>      | <b>2.39</b>  | <b>3.03</b>      |
|                          | <b>Serious</b> | <b>0.85</b>  | <b>1.53</b>      | <b>0.87</b>  | <b>1.28</b>      |
| <b>SMQ MACE (Narrow)</b> | <b>All</b>     | <b>1.17</b>  | <b>1.63</b>      | <b>1.21</b>  | <b>1.62</b>      |
|                          | <b>Serious</b> | <b>0.80</b>  | <b>1.53</b>      | <b>0.83</b>  | <b>1.28</b>      |
| <b>Custom MACE</b>       | <b>All</b>     | <b>0.69</b>  | <b>1.24</b>      | <b>0.73</b>  | <b>1.14</b>      |
|                          | <b>Serious</b> | <b>0.59</b>  | <b>1.15</b>      | <b>0.59</b>  | <b>1.01</b>      |

Incidence Rate (events / year\*100)

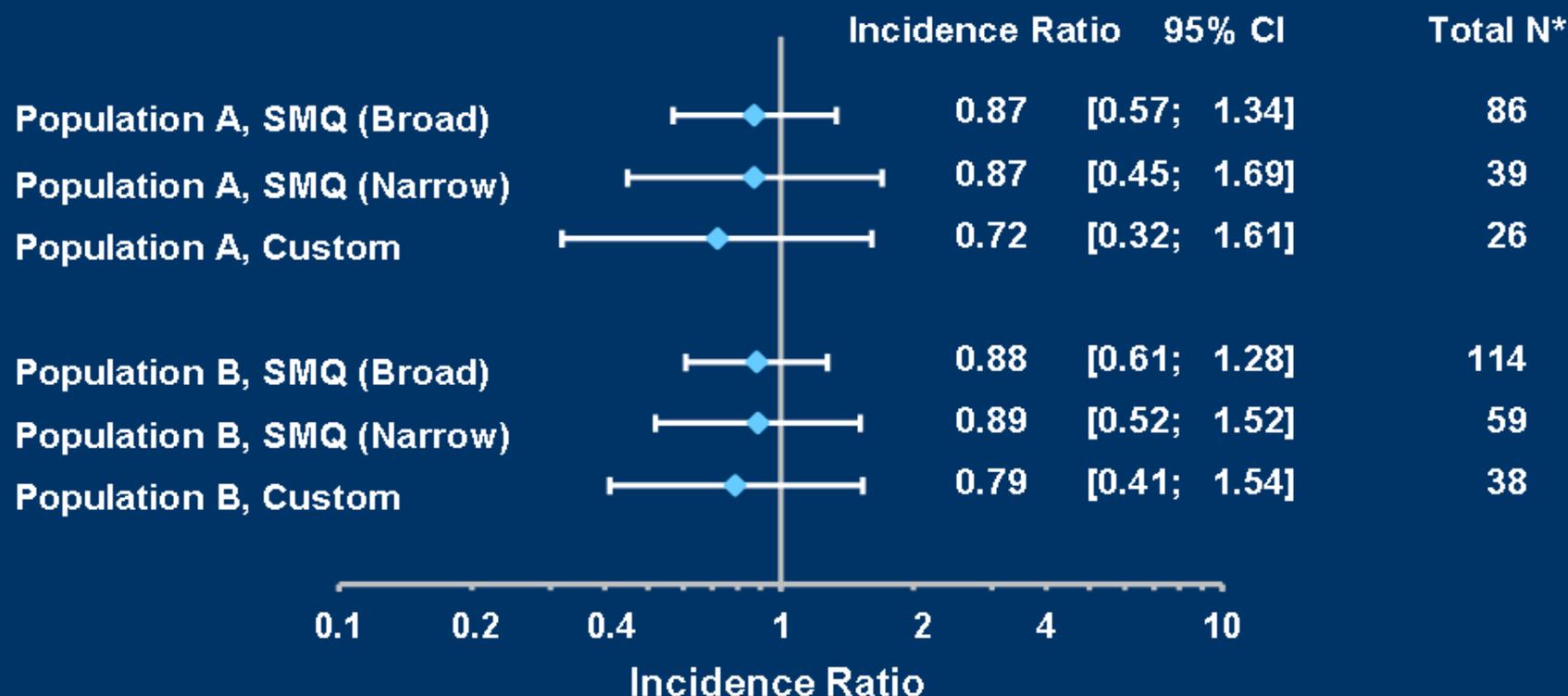
L- total liraglutide, TC – total comparator

# MACE Analysis – Comparators



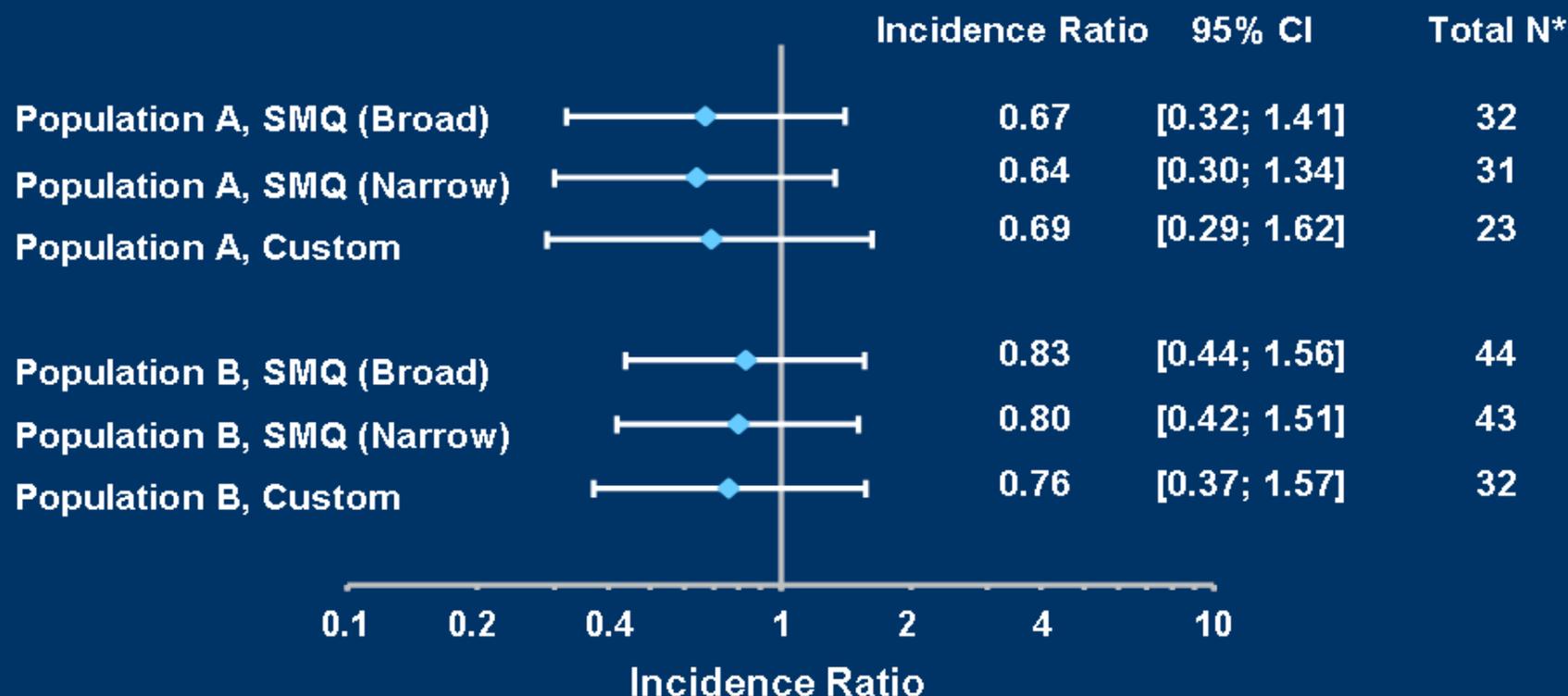
SU: sulfonylurea; MET: metformin; TZD: thiazolidinedione (rosiglitazone)

# MACE, Incidence Ratio, Pooled Data Liraglutide vs. Total Comparator – Stratified Analysis



\*Number of subjects with MACE: liraglutide + total comparator

# Serious MACE, Incidence Ratio, Pooled Data, Liraglutide vs. Total Comparator Stratified Analysis



\*Number of subjects with MACE: liraglutide + total comparator

# MACE Analysis – All Groups

## Point Estimates and Upper 95% CI

| Population   | Incidence ratio (liraglutide vs.) |                   |                  | Upper 95% CI |                   |                  |
|--------------|-----------------------------------|-------------------|------------------|--------------|-------------------|------------------|
|              | Placebo                           | Active comparator | Total comparator | Placebo      | Active comparator | Total comparator |
| A SMQ Narrow | 1.06                              | 0.79              | 0.87             | 3.02         | 1.69              | 1.69             |
| A SMQ Broad  | 1.04                              | 0.82              | 0.87             | 2.16         | 1.32              | 1.34             |
| A Custom     | 0.80                              | 0.68              | 0.72             | 2.83         | 1.66              | 1.61             |
| B SMQ Narrow | 1.11                              | 0.82              | 0.89             | 2.74         | 1.52              | 1.52             |
| B SMQ Broad  | 1.02                              | 0.85              | 0.88             | 1.92         | 1.29              | 1.28             |
| B Custom     | 0.92                              | 0.76              | 0.79             | 2.83         | 1.61              | 1.54             |



# Incidence Ratio Excluding Rosiglitazone Treated Subjects in Trial 1436, Total Liraglutide vs. Total Comparator

|              |                   |         | Original analysis  | Without RSG        |
|--------------|-------------------|---------|--------------------|--------------------|
| Population A | SMQ MACE (Narrow) | All     | 0.87 [ 0.45; 1.69] | 0.76 [ 0.39; 1.46] |
|              |                   | Serious | 0.64 [ 0.30; 1.34] | 0.58 [ 0.27; 1.22] |
| Population A | SMQ MACE (Broad)  | All     | 0.87 [ 0.57; 1.34] | 0.90 [ 0.57; 1.42] |
|              |                   | Serious | 0.67 [ 0.32; 1.41] | 0.62 [ 0.29; 1.29] |
| Population A | Custom MACE       | All     | 0.72 [ 0.32; 1.61] | 0.60 [ 0.27; 1.34] |
|              |                   | Serious | 0.69 [ 0.29; 1.62] | 0.61 [ 0.26; 1.44] |
| Population B | SMQ MACE (Narrow) | All     | 0.89 [ 0.52; 1.52] | 0.81 [ 0.48; 1.38] |
|              |                   | Serious | 0.80 [ 0.42; 1.51] | 0.75 [ 0.40; 1.41] |
| Population B | SMQ MACE (Broad)  | All     | 0.88 [ 0.61; 1.28] | 0.90 [ 0.61; 1.33] |
|              |                   | Serious | 0.83 [ 0.44; 1.56] | 0.78 [ 0.42; 1.46] |
| Population B | Custom MACE       | All     | 0.79 [ 0.41; 1.54] | 0.71 [ 0.37; 1.36] |
|              |                   | Serious | 0.76 [ 0.37; 1.57] | 0.70 [ 0.34; 1.44] |

Without Rosiglitazone (RSG): Excluding 5 Subjects with non-serious MACE in group SMQ Broad (no subjects in SMQ Narrow or Custom)

# Conclusion – Cardiovascular Safety

Given the limitations/strengths of analysis, we found:

- MACE analyses were consistent across a number of different populations and outcome definitions
- Total liraglutide vs. total control
  - All point estimates  $<1$
  - All upper 95% confidence intervals  $<1.8$

# Liraglutide Benefit/Risk and Risk Management Plan

Alan C. Moses, MD

Corporate Vice President  
Global Chief Medical Officer  
Novo Nordisk

# Liraglutide – Consistent with Revised ADA/EASD Treatment Algorithm

- **Effective glycemic control**
  - Major reduction in HbA<sub>1c</sub> from baseline
  - Greater HbA<sub>1c</sub> response vs. common diabetes therapies
- **Non-glycemic effects**
  - Weight loss, improved beta-cell function
- **Safety**
  - Low risk of hypoglycemia
- **Ease-of-use**
  - Once-daily dosing unrelated to meals

# Adverse Events of Special Interest

- C-cell findings
  - Limited to rats and mice
  - No abnormalities in non-human primates
  - No evidence of drug-induced C-cell activation in >5000 patients
- Papillary carcinoma of the thyroid
  - Incidental findings based on calcitonin screening program
- Pancreatitis
  - Small number of cases consistent with incidence rate in diabetes population

# Cardiovascular Evaluation of Liraglutide

- No prolongation of QT interval in human physiologic data
- No adverse effects on traditional biomarkers of CV risk
- Human clinical data
  - MACE analysis based on criteria requested by FDA and reported by FDA in their briefing document
    - Point estimates for liraglutide consistent across multiple analyses and  $<1.0$
    - Upper bounds of 95% confidence interval  $<1.8$  for active and total comparators

# Continued Risk Assessment

- Ongoing and planned Phase 3b program
  - 1800 additional subjects exposed or being exposed to liraglutide vs. additional diabetes comparator agents
    - Liraglutide vs. exenatide – completed
    - Liraglutide vs. sitagliptin – fully enrolled
    - Liraglutide with basal insulin detemir – enrolling
    - PK study in adolescents (ages 10–17)
    - Safety and efficacy in pediatric population (ages 10–17)
  - Allows for additional routine safety assessments in blinded, randomized trials

# Comprehensive Approach to Risk Management

- Labeling
- Post-marketing pharmacovigilance
- Post-marketing study commitments

# Post-marketing Pharmacovigilance

- AERS database to assess spontaneous reports of adverse events
- Large proactive claims safety surveillance data base study
  - Applying i3 Aperio system to assess signals from rare or infrequent events
  - Focus – thyroid and C-cell neoplasms, CV events, pancreatitis
  - Reporting to FDA/EMA regularly for 3–5 years
- Prospective post-approval CV outcomes study

# Cardiovascular Outcome Trial – Design and Endpoints

- Randomized, controlled, international
- 2 arms, parallel design
  - Liraglutide and placebo on background of “standard” therapy
- Entry criteria
  - 9,000 patients or more
  - High risk for cardiovascular disease
- Trial duration – minimum 3.5 years per subject
- CV endpoint adjudication committee and independent data safety monitoring board (DSMB)
- Primary endpoint
  - Designed to yield sufficient MACE events to exclude excess relative risk at 1.3 of CV death, non-fatal MI, or non-fatal stroke
- Additional safety endpoints

# Conclusions

- Liraglutide met primary regulatory endpoint
- Rapid and sustained improvements in both fasting, postprandial glucose levels led to substantial reduction in HbA<sub>1c</sub>
- Superior to several standard therapies in common use
- Met clinically important secondary endpoints consistent with revised ADA/EASD treatment algorithm for Type 2 diabetes
- Advantageous benefit/risk profile

# Liraglutide – Treatment of Type 2 Diabetes

FDA Advisory Committee Presentation

April 2, 2009