
What's new in diabetes management? A 15 minute update

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Disclosures

- ◆ Education and Research grants
 - Eli Lilly

Incretin Hormones and GLP-1 Agonists

New product launches

History: Incretin Effect and Incretin Hormones

◆ 1960s

- Researchers showed that glucose given orally produced a greater stimulation of insulin release than an equivalent dose of intravenous (IV) glucose
- Results suggested the presence of GI factors that augment the postprandial insulin response to ingested glucose

◆ 1969

- Unger and Eisentraut characterized the “intestinal secretion of insulin” as the incretin effect
- GI factors contributing to the incretin effect were named incretin hormones

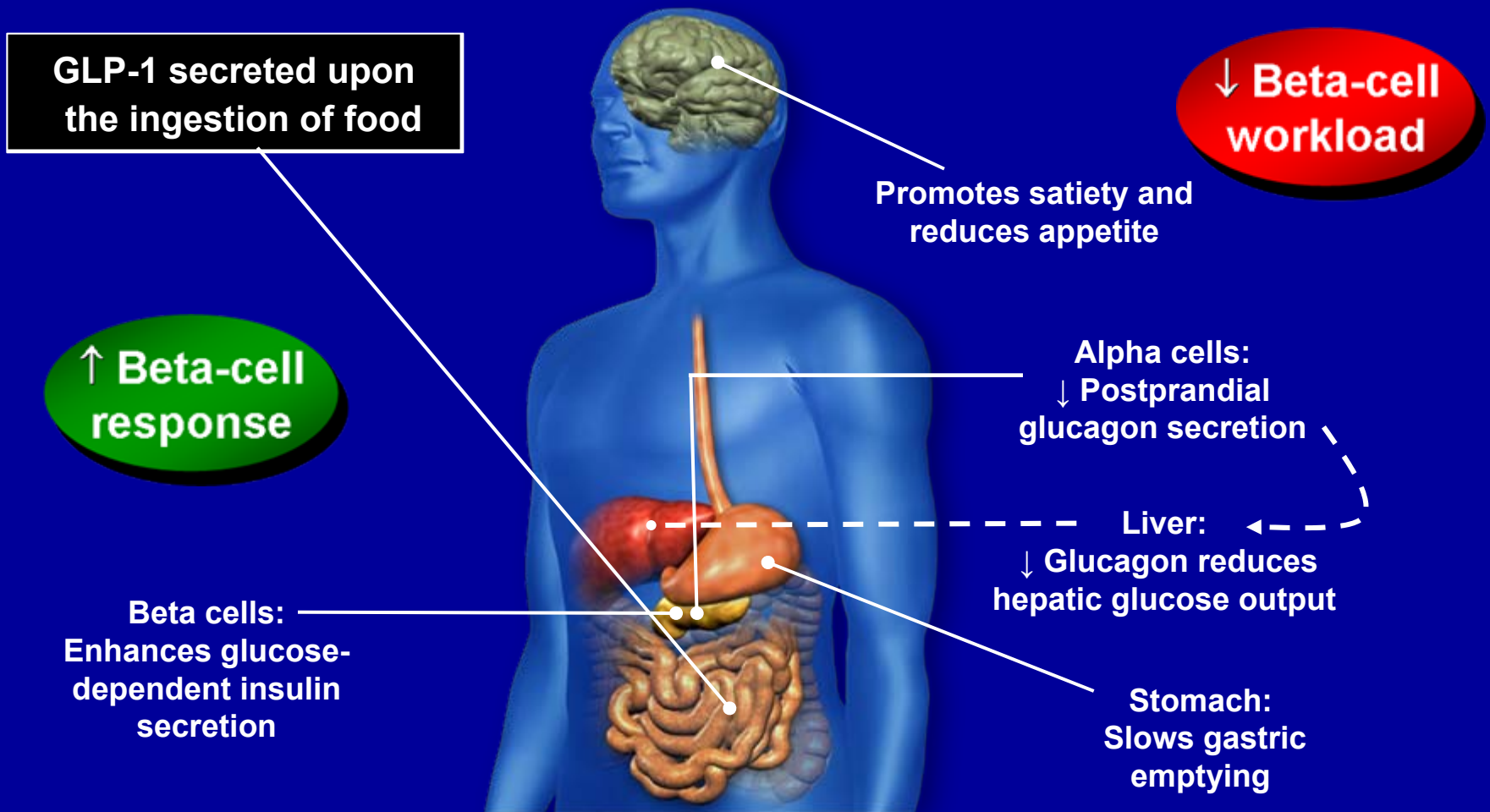
◆ 1970-1980s

- Glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) were identified

Incretin Hormone Physiological Functions

- ◆ Incretin hormones:
 - Are intestinal hormones that augment insulin secretion in response to nutrients
 - Are released from the small intestine endocrine cells in response to nutrient intake
 - Help the body respond with an appropriate postprandial insulin response following ingestion of a carbohydrate load

GLP-1 Effects in Humans: Understanding the Glucoregulatory Role of Incretins



Current GLP-1-Based Approaches for Improving Glycemic Control

- ◆ Agents that mimic the actions of GLP-1 (GLP-1 receptor agonists)
 - Exenatide
 - Liraglutide
- ◆ Agents that prolong the activity of endogenous GLP-1
 - DPP-4 inhibitors (sitagliptin, vildagliptin, saxagliptin)

Development of Exenatide: An Incretin Mimetic

Exenatide (Exendin-4)

- 1st in class GLP-1 agonist
- Synthetic version of salivary protein found in the Gila monster
- 53% homologous with human GLP-1
 - Binds to GLP-1 receptors on β cells
 - Resistant to DPP-4 inactivation



Site of DPP-4 Inactivation

Adapted from Nielsen LL, et al. *Regulatory Peptides*. 2004;117:77-88. With permission from Elsevier for English use only.
Drucker DJ. *Diabetes Care*. 2003;26:2929-2940.
Ahrén B. *Best Pract Res Clin Endocrinol Metab*. 2007;21:517-533.

The Glucoregulatory Actions of Exenatide

Summary of Placebo-controlled Data: Exenatide Improves Glycaemic Control with Associated Weight Loss

- ◆ Exenatide 10 µg BID, in 30-week Phase 3 clinical trials, in type 2 diabetes patients treated with MET and/or an SFU:
 - ↓ HbA_{1c} 0.8 to 0.9%
 - ↓ fasting and postprandial glucose
 - ↓ body weight 1.6-2.8 kg
- Similar results in combination with MET and/or SFU or MET and/or TZD
- Has also shown similar A1c improvements when compared to insulin glargine or biphasic insulin aspart
- These improved glycaemic effects were sustained over 3 years in open-label extensions, with progressive body weight reduction

Important Safety Information

BYETTA comes in an easy-to-use prefilled pen with premeasured doses for all patients.



◆ Indication (USA):

- ◆ As an adjunct to diet and exercise in adults with T2DM
- ◆ Product monograph lists approved use as monotherapy, or in combination with metformin, +/- sulphonylureas, or in combination with a TZD +/- metformin

◆ Administration:

- ◆ Initiate exenatide at 5 μg per dose BID for at least one month in order to improve tolerability
- ◆ Can then increase dose to 10 μg BID to further improve glycaemic control
- ◆ Administer within 60 minutes before meals

Exenatide Monotherapy: Hypoglycemia

- ◆ 5% (4/77), 4% (3/77), and 1% (1/77) of patients in the exenatide 5- μ g and 10- μ g and placebo groups, respectively, reported hypoglycemia ($P = \text{NS}$)
- ◆ No severe hypoglycemia occurred
- ◆ When exenatide was used in combination with a sulphonylurea, the incidence of hypoglycaemia was increased over that of placebo in combination with a sulphonylurea.

ITT sample (N=232); Statistical comparisons are for the combined exenatide group vs. placebo.

Moretto TJ, et al. *Clin Ther.* 2008;30(9):1448-1460.

BYETTA® European Union Summary of Product Characteristics, January 2008

Exenatide: Nausea

- ◆ **The most frequently reported adverse effect**
 - In patients treated with 5 µg or 10 µg of exenatide, generally 40-50% reported at least one episode of nausea
 - Most episodes were mild to moderate and occurred in a dose-dependent fashion
 - With continued therapy, the frequency and severity decreased in most patients who initially experienced it

Exenatide: Pancreatitis

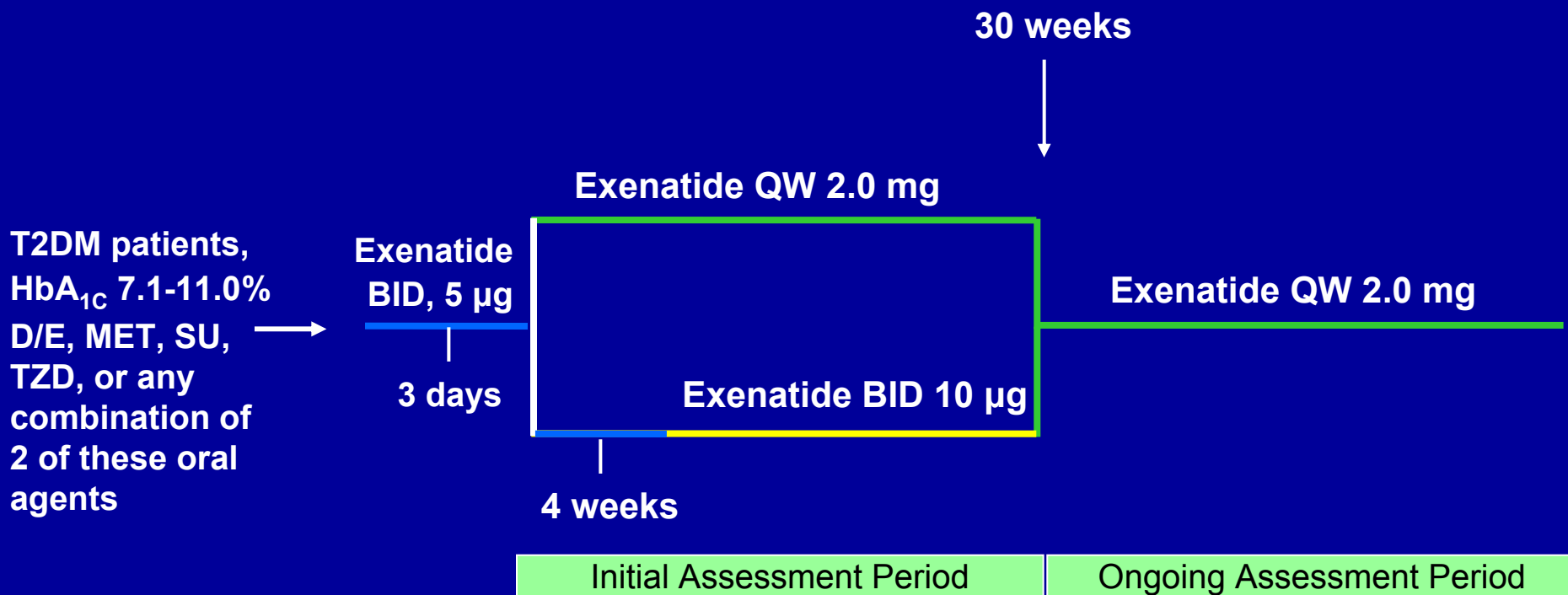
- ◆ Rare, spontaneously reported events have been identified primarily in postmarketing reports
 - ◆ Unknown if causal or coincidental, but association with GLP1 agonists can not be excluded
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Exenatide Monotherapy: Antibodies to Exenatide

- ◆ At endpoint, 27% and 28% of patients in the exenatide 5- μ g and 10- μ g groups, respectively, had detectable concentrations of antibodies to exenatide
- ◆ The presence of antibodies to exenatide had no clinically relevant effects on glycemic control or the safety profile

Once weekly exenatide

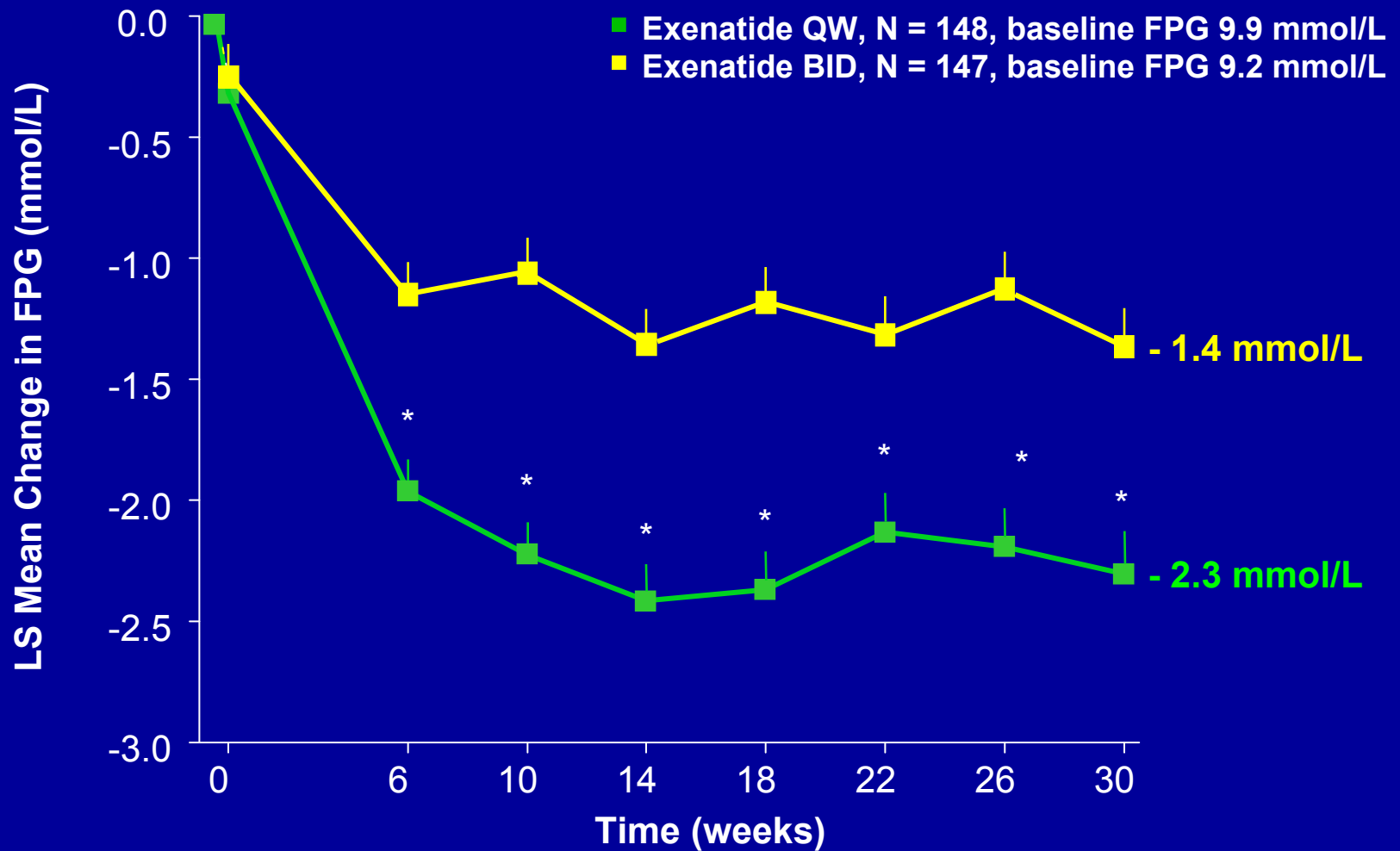
DURATION-1 Study Design



*DURATION: (Diabetes Therapy Utilization : Researching Changes in HbA_{1c}, Weight and Other Factors Through Intervention with Exenatide Once Weekly)

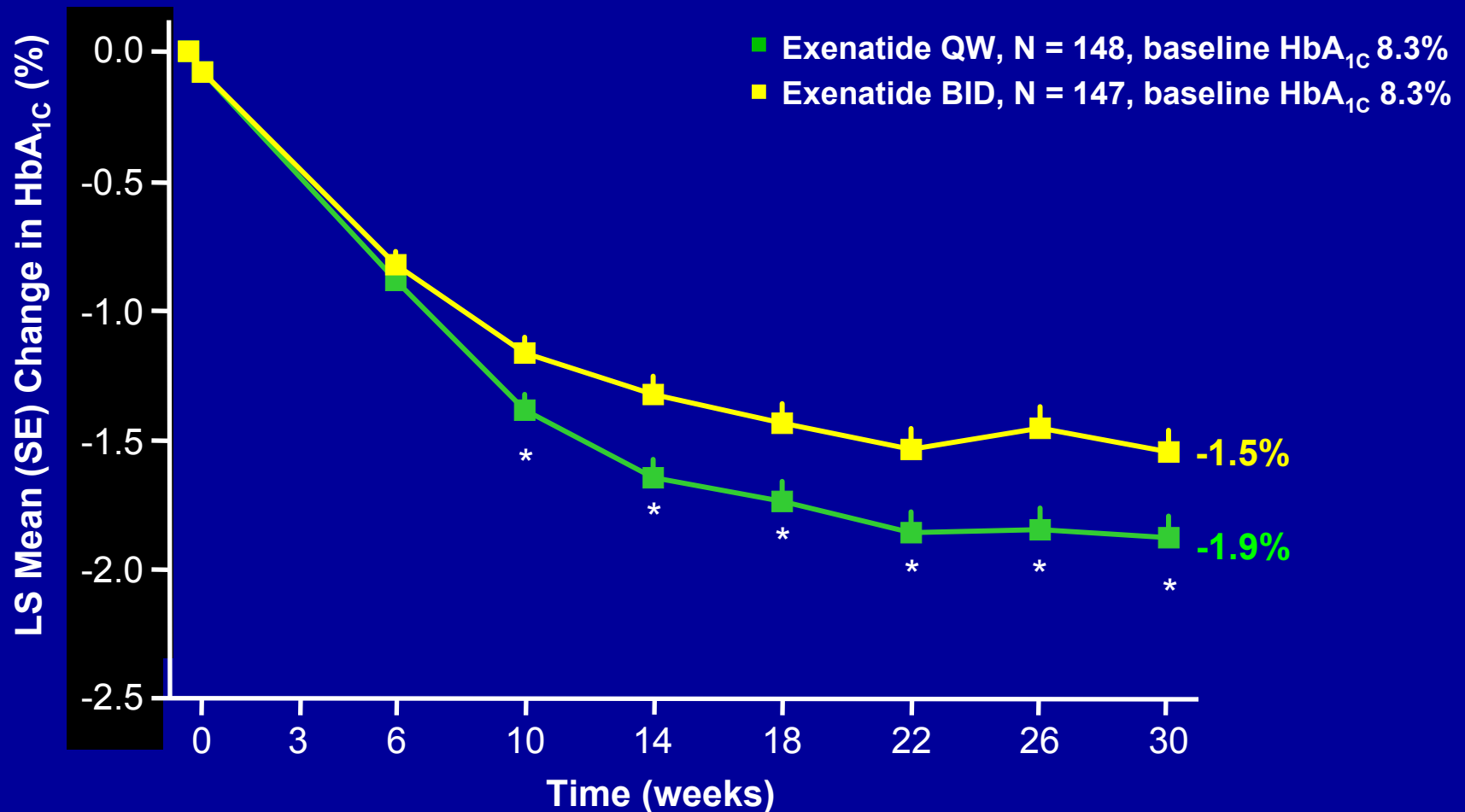
D/E = diet and exercise

Change in Fasting Plasma Glucose from Baseline over 30 Weeks



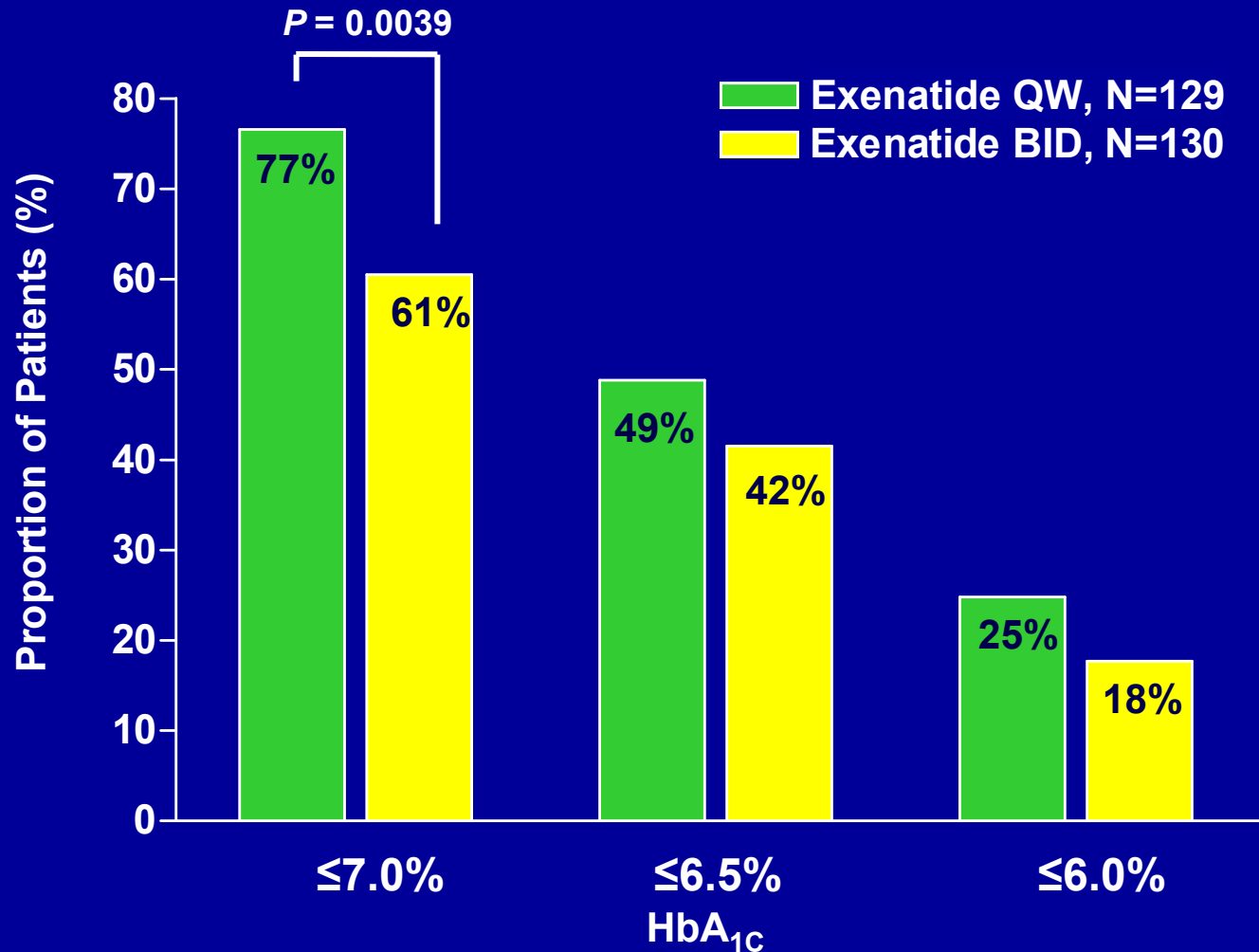
* $P \leq 0.0001$, exenatide QW vs. exenatide BID. ITT population, N=295.

Efficacy of Exenatide QW versus Exenatide BID: Change in HbA_{1c} from Baseline over 30 Weeks



* $P < 0.01$ for change from baseline exenatide QW vs. BID, $P = 0.0023$ for change from baseline exenatide QW vs. BID at 30 weeks. ITT population, $N=295$. LS = least square, SE = standard error.

Percentage of Evaluable Patients (N=259) Achieving HbA_{1c} ≤7.0%, ≤6.5%, ≤6.0% at Week 30



Evaluable population, N=259; $P=0.0039$, exenatide once weekly (QW) versus exenatide BID

Overall Incidence of Treatment-Emergent Adverse Events Occurring in 10% or More of Patients*

| | Exenatide QW N=148 | Exenatide BID N=145 |
|-----------------------------------|-----------------------|------------------------|
| Nausea | 26.4% | 34.5% |
| Vomiting | 10.8% | 18.6% |
| Injection site pruritus | 17.6% | 1.4% |
| Upper respiratory tract infection | 8.1% | 17.2% |
| Diarrhea | 13.5% | 13.1% |
| Constipation | 10.8% | 6.2% |
| Injection site bruising | 4.7% | 10.3% |
| Urinary tract infection | 10.1% | 8.3% |

* Patients received 1 or more doses of study drug
Frequent treatment-emergent adverse events with $\geq 10\%$ incidence

Percentage of Patients with Hypoglycemia*, by Treatment and Concomitant Sulfonylurea Use

| Hypoglycemia | Non-Sulfonylurea Background | | Sulfonylurea Background | |
|--------------|-----------------------------|-----------------------|-------------------------|-----------------------|
| | Exenatide QW N=93 | Exenatide BID N=93 | Exenatide QW N=55 | Exenatide BID N=54 |
| Major (%) | 0 | 0 | 0 | 0 |
| Minor (%) | 0 | 1.1% | 14.5% | 15.4% |

Major hypoglycemia: hypoglycemia that results in loss of consciousness, seizure, or coma which resolves after administration of glucagon or glucose, or requires third party assistance to resolve because of severe impairment in consciousness or behavior and has glucose value of <3.0 mmol/L.

Minor hypoglycemia: reported event that has symptoms consistent with hypoglycemia and a plasma glucose value of <3.0 mmol/L prior to treating the episode.

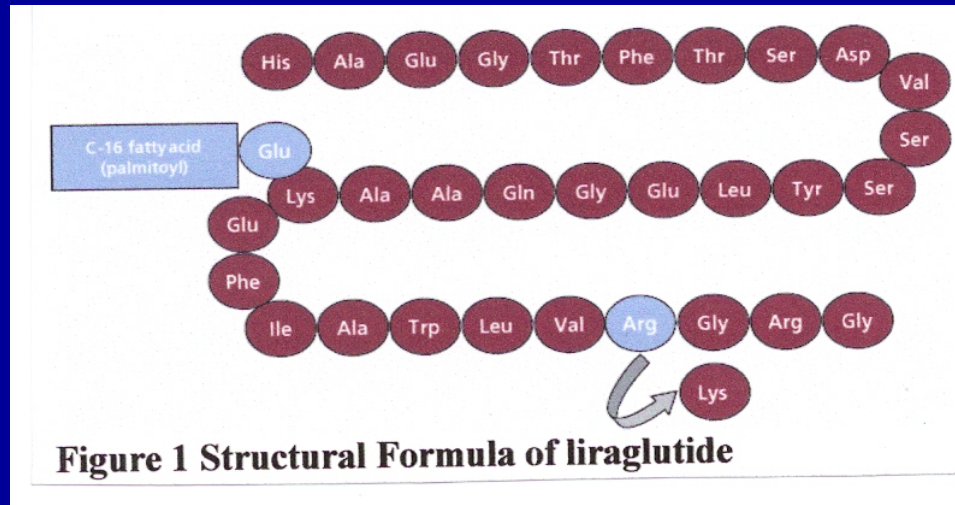
*at least one episode

DURATION-1 Study Conclusions

- ◆ Once weekly treatment with exenatide resulted in significant improvements in glycemic control compared to exenatide BID
- ◆ Once weekly exenatide did not show any ↑ risk of hypoglycemia
- ◆ Once weekly and twice daily exenatide showed similar reductions in body weight (3.7kg)
- ◆ Once weekly exenatide was generally well-tolerated

Liraglutide

- ◆ A synthetic GLP-1 analogue that is 97% homologous to GLP-1



- ◆ High degree of homology may partially explain the low levels of antibodies produced towards it
- ◆ A t_{1/2} of ~13h allows for once daily dosing

Liraglutide efficacy

Table 1. Comparison of Efficacy and Safety Outcomes in the LEAD-6 Study⁴⁸

| Outcome | Liraglutide Group ^a (n=233) | Exenatide Group ^b (n=231) | p Value |
|--|---|---|---------|
| Change in hemoglobin A _{1c} | -1.12% | -0.79% | 0.0001 |
| Hemoglobin A _{1c} < 7.0% | 54% of patients | 43% of patients | 0.0015 |
| Hemoglobin A _{1c} ≤ 6.5% | 35% of patients | 21% of patients | 0.0001 |
| Change in fasting plasma glucose level | -29 mg/dl | -11 mg/dl | 0.0001 |
| Change in body weight | -3.24 kg | -2.87 kg | NS |
| HOMA-B | 32.12% | 2.74% | 0.0001 |
| Minor hypoglycemia (no. of events/patient-year) | 1.932 | 2.600 | 0.0131 |

Data are mean unless otherwise indicated.

LEAD = Liraglutide Effect and Action in Diabetes; NS = not significant; HOMA-B = homeostatic model assessment.

^aLiraglutide 1.8 mg once/day.

^bExenatide 10 µg twice/day.

- ◆ Average reduction in A1c: 1 – 1.5%
- ◆ Decreases both FPG and PPG
- ◆ Average weight reduction: 3-4kg

Liraglutide Safety Information

◆ Indication (USA):

- ◆ As an adjunct to diet and exercise in adults with T2DM
- ◆ Product monograph describes studies showing efficacy when used as monotherapy, in combination with metformin, SU or both, or in combination with metformin + TZD

◆ Administration:

- ◆ Initiate liraglutide at 0.6mg/d for 1 week
- ◆ Then ↑ to 1.2mg/d up to 1.8mg/d to achieve glycemic control

Now available.



Liraglutide Safety Information

Adverse effects:

- ◆ **GI: nausea**, diarrhea, vomiting, constipation
 - Clinical trials show prevalence up to 30%
 - Dose dependant and transient → typically resolves in a few weeks
- ◆ **Hypoglycemia**: low overall frequency on its own
 - Similar frequency to other agents when used in combo (esp. with SU's)

Precautions:

- ◆ pancreatitis

◆ Contraindications:

- ◆ personal or family history of medullary thyroid carcinoma

Exenatide and Liraglutide

- ◆ There are no well-controlled studies in pregnant or breast feeding women

Drug Interactions:

- ◆ They delay gastric emptying so they may impair absorption of concomitantly administer oral medications
- ◆ Exenatide: postmarketing reports of increased INR

Final points...

- ◆ GLP-1 agonists are novel therapies which have been associated with:
 - Reduced FPG and PPG
 - Suppression of inappropriately high glucagon secretion
 - Improved β -cell responsiveness
 - Reduced food intake and weight loss
 - ◆ Exenatide BID and liraglutide are awaiting Health Canada approval
 - ◆
 - ◆ Exenatide once weekly is awaiting FDA approval
 - ◆ Place in therapy will become more defined with more clinical experience
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