Η ΘΕΣΗ ΤΩΝ ΑΓΩΝΙΣΤΩΝ ΤΩΝ GLP-1 ΥΠΟΔΟΧΕΩΝ ΣΤΟΝ ΑΛΓΟΡΙΘΜΟ ΤΗΣ ΑΝΤΙΔΙΑΒΗΤΙΚΗΣ ΘΕΡΑΠΕΙΑΣ

Ευάγγελος Λυμπερόπουλος

Αναπληρωτής Καθηγητής Παθολογίας Ιατρικής Σχολής Παν/μίου Ιωαννίνων

DISCLOSURES

➢ Participation in educational, research and advisory activities sponsored by:

ASTRA-ZENECA, VIANEX, MSD, LILLY, BAYER, AMGEN, ELPEN, SANOFI, MYLAN, BOEHRINGER-INGELHEIM, SPECIFAR, NOVARTIS, NOVO NORDISK, GALENICA, SERVIER, VALEANT
ΦΥΣΙΟΛΟΓΙΑ GLP-1
Figure 1 GLP-1 is released from the small intestine after meal ingestion and enhance glucose-stimulated insulin secretion (incretin action).
Figure 2 Pleitropic effects of GLP-1 or GLP-1R agonists (Adapted from references [24]).
ΑΓΩΝΙΣΤΕΣ ΑΓΩΝΙΣΤΕΣ ΑΓΩΝΙΣΤΕΣ GLP-1 ΥΠΟΔΟΧΕΩΝ
Μοριακή δομή των GLP-1 RAs

**Native human GLP-1**

**Liraglutide**  
97% amino acid homology to human GLP-1

**Exenatide**  
53% amino acid homology to human GLP-1

**Lixisenatide**  
50% amino acid homology to human GLP-1

## GLP-1RAs - φαρμακοκινητική

<table>
<thead>
<tr>
<th>Κατηγορία</th>
<th>Σκεύασμα</th>
<th>Χρόνος ημίσειας ζωής</th>
<th>Cmax</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ταχείας δράσης &lt;24 ώρες</td>
<td>Exanetide BD</td>
<td>2.4 ώρες</td>
<td>2 ώρες</td>
</tr>
<tr>
<td></td>
<td>Lixisenatide OD</td>
<td>2.7-4.3 ώρες</td>
<td>1.25-2.25 ώρες</td>
</tr>
<tr>
<td>Μακράς δράσης ≥24 ώρες</td>
<td>Liraglutide OD</td>
<td>13 ώρες</td>
<td>8-12 ώρες</td>
</tr>
<tr>
<td></td>
<td>Dulaglutide OW</td>
<td>90 ώρες</td>
<td>24-48 ώρες</td>
</tr>
<tr>
<td></td>
<td>Albiglutide OW</td>
<td>6-7 ημέρες</td>
<td>3-5 ημέρες</td>
</tr>
<tr>
<td></td>
<td>Exanetide OW</td>
<td>7-14 ημέρες</td>
<td>6-7 εβδομάδες</td>
</tr>
</tbody>
</table>

BD: twice a day; Cmax: maximum concentration; GLP-1RA: glucagon-like peptide-1 receptor agonist; OD: once a day; OW: once weekly
Υπάρχουν 2 τύποι των Αγωνιστών του Υποδοχέα του GLP-1 που επηρεάζουν σε διαφορετικό βαθμό, τη FPG και τη PPG.

### Glucose Reduction

**DPP-4 Inhibitors, GLP-1 Receptor Agonists, and SGLT2 Inhibitors Added to Metformin (Absolute Changes from Baseline; Not Head-to-Head Trials)**

<table>
<thead>
<tr>
<th>Baseline A1C (%)</th>
<th>DPP-4 Inhibitors</th>
<th>GLP-1 Receptor Agonists</th>
<th>SGLT2 Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alo1</td>
<td>Lin2</td>
<td>Sax3</td>
</tr>
<tr>
<td></td>
<td>7.9</td>
<td>8.1</td>
<td>8.1</td>
</tr>
<tr>
<td>Δ A1C (%)</td>
<td>-0.6</td>
<td>-0.5</td>
<td>-0.7</td>
</tr>
</tbody>
</table>

## Hypoglycemia with GLP-1 Receptor Agonists

### Percentage of Patients Reporting Hypoglycemia (Not Head-to-Head Trials)

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Add-on to Metformin</th>
<th>Add-on to SU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Dul&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Exe&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
<tr>
<td>0</td>
<td>4.0</td>
<td>5.2</td>
</tr>
</tbody>
</table>

*Metformin with or without SU or TZD. †Metformin with or without SU.

Weight Change with GLP-1 Receptor Agonists

Absolute Change from Baseline (Not Head-to-Head Trials)

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>Add-on to Metformin</th>
<th>Add-on to SU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alb¹</td>
<td>Alb⁶</td>
<td>Alb¹¹,*</td>
</tr>
<tr>
<td>Dul²</td>
<td>Dul⁷</td>
<td>Exe¹²</td>
</tr>
<tr>
<td>Exe³</td>
<td>Exe⁸</td>
<td>Exe¹³,†</td>
</tr>
<tr>
<td>Exe ER⁴</td>
<td>Exe ER⁹</td>
<td>Lir¹⁴</td>
</tr>
<tr>
<td>Lir⁵</td>
<td>Lir¹⁰</td>
<td></td>
</tr>
</tbody>
</table>

Δ Weight (kg)

-0.9  -2.3  -3.1  -3.1
-2.5  -2.6  -2.8  -2.6
-1.2  -1.6  -0.6  -0.2

*Metformin with or without SU or TZD. †Metformin with or without SU.

## Effects of Antihyperglycemic Therapies on Blood Pressure

### Meta-analyses

<table>
<thead>
<tr>
<th>Class</th>
<th>∆ Systolic BP, mmHg (95% CI)</th>
<th>∆ Diastolic BP, mmHg (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Newer therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLP-1 receptor agonists¹</td>
<td>-3.57 (-5.49 to -1.66)</td>
<td>-1.38 (-2.02 to -0.73)</td>
</tr>
<tr>
<td>DPP-4 inhibitors²</td>
<td>-0.1 (-1.2 to 0.8)</td>
<td>—</td>
</tr>
<tr>
<td>SGLT2 inhibitors³</td>
<td>-3.77 (-4.65 to -2.90)</td>
<td>-1.75 (-2.27 to -1.23)</td>
</tr>
<tr>
<td><strong>Older therapies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin⁴</td>
<td>-1.09 (-3.01 to 0.82)</td>
<td>-0.97 (-2.15 to 0.21)</td>
</tr>
<tr>
<td>TZDs⁵</td>
<td>-4.70 (-6.13 to -3.27)</td>
<td>-3.79 (-5.82 to -1.77)</td>
</tr>
</tbody>
</table>

Strategies to Minimize the Occurrence of Nausea

• Titrate the dose slowly

• Educate patients on feeling of satiety (due to delayed gastric emptying)

• Patients should eat slower

• Avoid administering a GLP-1 RA close to a large or high-fat meal

GLP-1 RAs: Renal Impairment

- Renal impairment with GLP-1 RAs has been reported, usually in association with hypovolemia due to nausea, vomiting, diarrhea, or dehydration
- Use in caution with patients with renal impairment, especially when initiating or escalating doses
- Exenatide and exenatide-LAR should not be used in patients with CrCl <30 mL/min

CrCl = creatinine clearance

MHRA. http://www.mhra.gov.uk/Safetyinformation/DrugSafetyUpdate/CON088117
Warnings and Precautions with GLP-1 Receptor Agonists

Thyroid Cancer

- Thyroid C-cell tumors observed in rodents
- Unknown whether GLP-1 receptor agonists cause these tumors, including medullary thyroid carcinoma, in humans
- GLP-1 receptor agonists should not be used in patients with
  - Personal or family history of medullary thyroid carcinoma
  - Multiple endocrine neoplasia type 2

Bydureon® PI 2014.[21]
Tanzeum™ PI 2014.[23]
Trulicity™ PI 2014.[24]
Victoza® PI 2013.[25]
Ι. ΛΙΣΙΞΕΝΑΤΙΔΗ (LYXUMIA®)
Η Λιξισενατίδη προκάλεσε συγκρίσιμες μειώσεις στην HbA1c σε όλες τις κλινικές μελέτες

BI = Βασική ινσουλίνη
IG = Ινσουλίνη Glargine
M = Μετφορμίνη
P = Πιογλιταζόνη
SU = Σουλφονυλουρία

Διάρκεια Διαβήτη (έτη) 1.4/1.1/1.4
Αρχική τιμή HbA1C (%) 8/8.1/8.1
Αρχική τιμή μέσο ωμέγα-3 (Kg) 89.0/86.5/86.1
Αρχική τιμή μέσου σωματικού βάρους (Kg/m²) 32.3/31.6/31.8
Βασική θεραπεία None
Διάρκεια μελέτης (Εβδομάδες) 12

Note: All Lixisenatide dosing is 1-step AM regimen, unless otherwise noted
Source: GetGoal Clinical Program,
ELIXA: Study Design

Patients with T2DM and an ACS event

Run-in period: 10 μg lixisenatide (0.10 mL injection), once daily

Titration period: 10 μg lixisenatide (0.10 mL injection), once daily

Maintenance period: 20 μg lixisenatide (0.20 mL injection), once daily

Run-in period: 10 μg volume-matched placebo (0.10 mL injection), once daily

Titration: 10 μg volume-matched placebo (0.10 mL injection), once daily

Maintenance period: 20 μg volume-matched placebo (0.20 mL injection), once daily

Primary End Points
Time to first occurrence of the primary CV event: CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA

ELIXA: Primary Outcome

Primary Composite CV Outcome

HR = 1.02
95% CI: 0.89-1.17

Lixisenatide (n=3034)
Placebo (n=3034)

Heart rate was unaffected by lixisenatide, although there was an early increase of 0.4 beats/min that was not present by the end of the study.

ELIXA: Hospitalization for HF

Hospitalization for HF

Hazard ratio = 0.95
95% CI: 0.75-1.23

Lixisenatide (n=3034)
Placebo (n=3034)

ΛΙΞΙΣΕΝΑΤΙΔΗ
Σημειώσεις από την ΠΧΠ

4.1 Θεραπευτικές ενδείξεις

Το Λυκυμία ενδείκνυται για τη θεραπεία ενηλίκων με σακχάρωδη διαβήτη τύπου 2 για την επίτευξη γλυκαιμικού ελέγχου σε συνδυασμό με από του στόματος χορηγούμενα φαρμακευτικά προϊόντα για τη μείωση του σακχάρου ή και με βασική νυσουλίνη όταν αυτά από κοινού με διαίτα και άσκηση δεν παρέχουν επαρκή γλυκαιμικό ελέγχο (βλέπε παραγράφους 4.4 και 5.1 σχετικά με τα διαθέσιμα στοιχεία για τους διαφορετικούς συνδυασμούς).

- **ΠΡΑΣΙΝΗ ΠΕΝΑ**: Κάθε δόση 0,2 mL περιέχει 10 μg Λιξισενατίδης. Η δόση αρχίζει με 10 μg Λιξισενατίδης εφάπαξ ημερησίως για 14 ημέρες.
- **ΒΥΣΣΙΝΙ (ΜΠΟΡΝΤΩ) ΠΕΝΑ**: Κάθε δόση 0,2 mL περιέχει 20 μg Λιξισενατίδης. Μια σταθερή δόση συντήρησης των 20 μg Λιξισενατίδης εφάπαξ ημερησίως αρχίζει από τη 15η ημέρα.
- Το Λυκυμία χορηγείται εφάπαξ ημερησίως, εντός της ώρας πριν από οποιοδήποτε γεύμα της ημέρας. Είναι προτιμότερο η γευματική ένεση του Λυκυμία να γίνεται πριν από το ίδιο γεύμα κάθε ημέρα, όταν το πιο βολικό γεύμα έχει επιλεγεί. Εάν παραλειφθεί μία δόση Λυκυμία, πρέπει να χορηγηθεί εντός της ώρας πριν από το επόμενο γεύμα.
- Δεν απαιτείται προσαρμογή της δοσολογίας σε ηλικιωμένους άνω των 65 ετών, σε ήπια νεφρική δυσλειτουργία (CLcr 50-80 mL/min) ή σε ηπατική δυσλειτουργία.
- Σε μέτρια νεφρική δυσλειτουργία (CLcr 30-50 mL/min), πρέπει να χρησιμοποιείται με προσοχή, ενώ σε σοβαρή νεφρική δυσλειτουργία (CLcr < 30 mL/min) και σε νεφροπάθεια τελικού σταδίου δεν συνιστάται η χρήση του Λυκυμία®.
II. ΛΙΡΑΓΛΟΥΤΙΔΗ (VICTOZA®)
GLP-1RA head-to-head συγκριτικές μελέτες: μεταβολή της HbA1c

Baseline HbA1c:

<table>
<thead>
<tr>
<th></th>
<th>LEAD-6</th>
<th>DURATION-6</th>
<th>HARMONY-7</th>
<th>AWARD-6</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8.2%</td>
<td>8.4%</td>
<td>8.2%</td>
<td>8.1%</td>
</tr>
<tr>
<td></td>
<td>8.1%</td>
<td>8.5%</td>
<td>8.2%</td>
<td>8.1%</td>
</tr>
</tbody>
</table>

Change in HbA1c (%)

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide 1.8 mg</th>
<th>Exenatide BID</th>
<th>Exenatide OW</th>
<th>Albiglutide 50 mg OW</th>
<th>Dulaglutide 1.5 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAD-6</td>
<td>-1.12</td>
<td>-0.79</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DURATION-6</td>
<td>1.48</td>
<td>-1.28</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HARMONY-7</td>
<td>-0.99</td>
<td>-0.78</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AWARD-6</td>
<td></td>
<td></td>
<td>-0.85</td>
<td></td>
<td>-1.36</td>
</tr>
</tbody>
</table>

Nominal 95% CI = −0.06 (−0.19; 0.07), p<0.0001 for non-inferiority vs. liraglutide

p<0.0001 for non-inferiority vs. liraglutide
GLP-1RA head-to-head συγκριτικές μελέτες: σωματικό βάρος

Baseline body weight (kg):
- **LEAD-6**: 93.1 - 93.0
- **DURATION-6**: 91.1 - 90.9
- **HARMONY-7**: 92.8 - 91.7
- **AWARD-6**: 94.4 - 93.8

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LEAD-6</th>
<th>DURATION-6</th>
<th>HARMONY-7</th>
<th>AWARD-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide 1.8 mg</td>
<td>-3.2</td>
<td>-2.9</td>
<td>p=0.22</td>
<td></td>
</tr>
<tr>
<td>Exenatide BID</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Exenatide OW</td>
<td>-3.6</td>
<td>-2.7</td>
<td>p=0.0005</td>
<td></td>
</tr>
<tr>
<td>Albiglutide 50 mg OW</td>
<td>-2.2</td>
<td></td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Dulaglutide 1.5 mg</td>
<td></td>
<td>-2.9</td>
<td>p=0.011</td>
<td></td>
</tr>
</tbody>
</table>
LEADER designed to investigate cardiovascular profile of liraglutide versus standard of care

LEADER trial design

9,340 patients with T2DM

Standard of care + liraglutide (0.6-1.8 mg once daily)

Standard of care + placebo (daily blinded injection)

Primary end-point

- **Primary end-point:**
  - Time from randomisation to composite outcome ie first occurrence of:
    - CV death
    - Non-fatal myocardial infarction (MI)
    - Non-fatal stroke

Key inclusion criteria

- Adults above 50 years with T2DM and established cardiovascular disease, or above 60 years with multiple cardiovascular risk factors
- HbA$_{1c}$ $\geq$7.0%
LEADER: Primary Outcome*

HR: 0.87
95% CI (0.78-0.97)
\(P < .001\) for noninferiority
\(P = .01\) for superiority

13%

No. at Risk

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
<th>42</th>
<th>48</th>
<th>54</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liraglutide</td>
<td>4668</td>
<td>4593</td>
<td>4496</td>
<td>4400</td>
<td>4280</td>
<td>4172</td>
<td>4072</td>
<td>3982</td>
<td>1562</td>
<td>424</td>
</tr>
<tr>
<td>Placebo</td>
<td>4672</td>
<td>4588</td>
<td>4473</td>
<td>4352</td>
<td>4237</td>
<td>4123</td>
<td>4010</td>
<td>3914</td>
<td>1543</td>
<td>407</td>
</tr>
</tbody>
</table>

*3-point MACE consisting of CV death, nonfatal MI, or nonfatal stroke

LEADER: CV Death

HR: 0.78
95% CI (0.66-0.93)
P = .007

22%

LEADER: All-Cause Death

HR: 0.85
95% CI (0.74-0.97)
\( P = .02 \)

15%

LEADER: Hospitalization for HF

HR: 0.87
95% CI (0.73-1.05)
P = .14

Effects of Liraglutide on Clinical Stability Among Patients With Advanced Heart Failure and Reduced Ejection Fraction
A Randomized Clinical Trial

DESIGN, SETTING, AND PARTICIPANTS  Phase 2, double-blind, placebo-controlled randomized clinical trial of patients with established heart failure and reduced LVEF who were recently hospitalized. Patients were enrolled between August 2013 and March 2015 at 24 US sites.

INTERVENTIONS  The GLP-1 agonist liraglutide (n = 154) or placebo (n = 146) via a daily subcutaneous injection; study drug was advanced to a dosage of 1.8 mg/d during the first 30 days as tolerated and continued for 180 days.

<table>
<thead>
<tr>
<th>Type 2 diabetes mellitus</th>
<th>91 (59)</th>
<th>87 (60)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>25 (20-33)</td>
<td>25 (19-32)</td>
</tr>
</tbody>
</table>

[A] Time to death

[B] Time to death or rehospitalization for heart failure

**A**

HR, 1.10 (95% CI, 0.57-2.14); log-rank P = .78

**B**

HR, 1.30 (95% CI, 0.92-1.83); log-rank P = .14
Novo Nordisk receives positive 17-2 vote from FDA Advisory Committee that Victoza® provides substantial evidence of cardiovascular risk reduction in patients with type 2 diabetes

PLAINSBORO, N.J., June 20, 2017 /PRNewswire/ -- Novo Nordisk today announced that the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the US Food and Drug Administration (FDA) has completed its meeting regarding the supplemental New Drug Application (sNDA) for inclusion of the data from the cardiovascular outcomes trial LEADER in the label of Victoza® (liraglutide) injection 1.2 mg or 1.8 mg.

The discussions at the Advisory Committee meeting were based on data from the LEADER trial, which involved more than 9,300 people with type 2 diabetes at high risk of major cardiovascular events.

The Advisory Committee voted unanimously 19-0 in favor of Victoza® on the question: "Do the results of LEADER establish that use of Victoza® in patients with type 2 diabetes is not associated with excess cardiovascular risk?"

The Advisory Committee voted 17-2 in favor of Victoza® on the question: "Does the LEADER trial provide the substantial evidence needed to establish that Victoza® (liraglutide) 1.8 mg reduces cardiovascular risk in patients with type 2 diabetes?"
**Novo Nordisk A/S: Victoza® has been approved in the EU as the only GLP-1 with a label to include prevention of cardiovascular events**

**Bagsværd, Denmark, 27 July 2017 -** The European Commission has approved an update to the Victoza® (liraglutide) EU label that expands the indication to reflect both improving blood sugar and cardiovascular (CV) events as integral parts of type 2 diabetes treatment. Victoza® is the only GLP-1 that is proven to prevent CV events in people with type 2 diabetes and high CV risk.

The updated label includes results from the LEADER trial, which demonstrated that Victoza® statistically significantly reduced the risk of cardiovascular death, non-fatal myocardial infarction (heart attack) or non-fatal stroke by 13% versus placebo, when added to standard of care. The overall risk reduction was derived from a statistically significant 22% reduction in cardiovascular death with Victoza® treatment versus placebo and non-significant reductions in non-fatal myocardial infarction and non-fatal stroke.

"Cardiovascular disease is the number one cause of death for people with type 2 diabetes and requires treatment strategies that can tackle both blood glucose and cardiovascular risk to help improve outcomes," said Mads Krogsgaard Thomsen, executive vice president and chief science officer of Novo Nordisk. "The European Commission’s approval of the expanded Victoza® label enables physicians to provide their patients with the only GLP-1 proven to prevent cardiovascular events in people with type 2 diabetes and high cardiovascular risk."
Liraglutide and Renal Outcomes in Type 2 Diabetes

**B New Onset of Persistent Macroalbuminuria**

Hazard ratio, 0.74 (95% CI, 0.60–0.91)  
P=0.004

26%

**C Persistent Doubling of Serum Creatinine Level**

Hazard ratio, 0.89 (95% CI, 0.67–1.19)  
P=0.43

**D Continuous Renal-Replacement Therapy**

Hazard ratio, 0.87 (95% CI, 0.61–1.24)  
P=0.44
## LEADER: Selected AEs of Special Interest

<table>
<thead>
<tr>
<th></th>
<th>Number of patients</th>
<th>Liraglutide</th>
<th>Placebo</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gallstone disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute gallstone disease</td>
<td>145</td>
<td>90</td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cholelithiasis</td>
<td>68</td>
<td>50</td>
<td></td>
<td>.09</td>
</tr>
<tr>
<td>Acute cholecystitis</td>
<td>36</td>
<td>21</td>
<td></td>
<td>0.46</td>
</tr>
<tr>
<td><strong>Thyroid events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>44</td>
<td>33</td>
<td></td>
<td>.21</td>
</tr>
<tr>
<td>Hyperthyroidism</td>
<td>13</td>
<td>8</td>
<td></td>
<td>.27</td>
</tr>
<tr>
<td><strong>Diabetic foot ulcer</strong></td>
<td>181</td>
<td>198</td>
<td></td>
<td>.38</td>
</tr>
<tr>
<td><strong>Immunogenicity events</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>59</td>
<td>44</td>
<td></td>
<td>.14</td>
</tr>
<tr>
<td>Injection site reactions</td>
<td>32</td>
<td>12</td>
<td></td>
<td>.0002</td>
</tr>
</tbody>
</table>

0.6 mg → 1.2 mg → 1.8 mg
ΛΙΡΑΓΛΟΥΤΙΔΗ 3.0 mg (SAXENDA®)
SCALE: Change in Body Weight (%), Liraglutide vs Placebo

Baseline weight: 106 kg

*Statistical analysis is ANCOVA.
III. ΕΞΕΝΑΤΙΔΗ ΛΑΡ (BYDUREON®)
Glucose Control With Exenatide ER

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Add-on to OAs* 30 Weeks¹</th>
<th>Monotherapy vs OAs 26 Weeks²</th>
<th>Add-on to Metformin 26 Weeks³</th>
<th>Add-on to Met +/- SU 26 Weeks⁴</th>
<th>Add-on to OAs† 26 Weeks⁵</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>258</td>
<td>820</td>
<td>514</td>
<td>456</td>
<td>911</td>
</tr>
<tr>
<td>Baseline A1C (%)</td>
<td>8.3 8.3</td>
<td>8.5 8.5 8.6 8.5</td>
<td>8.5 8.5 8.6</td>
<td>8.3 8.3</td>
<td>8.4 8.5</td>
</tr>
</tbody>
</table>

| Δ A1C (%)                  | -1.5 -1.90                | -1.15 -1.63 -1.48 -1.53     | -0.9 -1.20                    | -1.3 -1.50                     | -1.48 -1.28               |
|                           | **P<0.01**                | **P<0.001**                 | **P<0.0001**                  | **P=0.017**                    | **P=0.02**                |

*Metformin, sulfonylurea, thiazolidinedione, or combination of any 2 of these agents.
†Metformin, sulfonylurea, metformin + sulfonylurea, or metformin + pioglitazone.

DURATION-8: a 28-Week, Διπλή τυφλή μελέτη placebo controlled, Phase III Study

Key Inclusion Criteria:
- ≥18 y; T2D;
- A1C 8-12%; stable dose MET ≥2 mo

1:1 Randomization

Primary Endpoint
- Change in A1C from baseline

Secondary Endpoints Included
- Change in body weight
- Change in FPG
- Change in 2-hour PPG
- Proportion of patients achieving A1C <7%
- Proportion of patients achieving weight loss ≥5%
- Change in seated SBP

Exploratory Endpoints Included
- Change in A1C by baseline A1C
- Change in weight by baseline A1C

N=695*

* Includes 1 patient who was wrongly randomized but did not receive treatment.

Note: Study was not powered to compare the individual treatment of EQW alone and DAPA alone.

Εβδομαδιαία Εξενατίδη + Νταπαγλιφλοζίνη
Σημαντική ελάττωση της A1C σε 28 εβδομάδες

 alters A1C by 2.0% in 28 weeks

EQW + DAPA (n=228); BL, 9.3%
EQW (n=227); BL, 9.3%
DAPA (n=230); BL, 9.3%

* Difference, p<0.05 vs. EQW; † Difference, p<0.05 vs. DAPA; ‡ Difference, p=0.004; § Difference, p<0.001.
Note: Data is least squares mean change. Error bars show standard errors. Analyzed in the ITT population.
Εβδομαδιαία Εξενατίδη + Νταπαγλιφλοζίνη
Σημαντική ελάττωση του σωματικού βάρους σε 28 εβδομάδες

EQW + DAPA (n=228); BL, 91.8 kg
EQW (n=227); BL, 89.8 kg
DAPA (n=230); BL, 91.1 kg

* Difference, p<0.05 vs. EQW; † Difference, p<0.05 vs. DAPA; ‡ Difference, p=0.002; § Difference, p=0.002.
Note: Data is least squares mean change. Error bars show standard errors. Analyzed in the ITT population.
Εβδομαδιαία Εξενατίδη + Νταπαγλιφλοζίνη σημαντική ελάττωση στην αρτηριακή πίεση την εβδομάδα 28

<table>
<thead>
<tr>
<th></th>
<th>EQW + DAPA</th>
<th>EQW</th>
<th>DAPA</th>
</tr>
</thead>
<tbody>
<tr>
<td>BL, mm Hg</td>
<td>-2.9</td>
<td>-2.4</td>
<td>-1.8</td>
</tr>
<tr>
<td>Change, mm Hg</td>
<td>-4.2</td>
<td>-1.3</td>
<td>-1.8</td>
</tr>
</tbody>
</table>

* Difference, p<0.05.
Note: Data is least squares mean change. Analyzed in the ITT population.
EXSCEL: Study Design

14,752 Patients

EXENATIDE ONCE WEEKLY

PLACEBO ONCE WEEKLY

Randomisation (double blind)

1w 2m 6m 1y

Visits every 6 months

End of Treatment

Minimum 1360 primary events

Safety Follow-up (70-days)

Aim is for glycaemic equipoise

Key Inclusion Criteria
- T2DM, HbA1c 6.5-10% (inclusive)
- Anti-DM drug naïve, oral agents and/or insulin
- ≥18 years old
- Any level of CV risk
- ~70% with prior CV event
  - Prior coronary, cerebrovascular or peripheral vascular event or stenosis

Key Exclusion Criteria
- T1DM
- ≥2 episodes of severe hypoglycaemia within 12 months
- Current or prior GLP1-RA
- eGFR <30mL/min/1.73m²
- Prior pancreatitis
- Personal or familial history of MEN-2
- Baseline calcitonin >40ng/L
Primary Composite Cardiovascular Outcome

Intention-to-Treat Analysis for Non-inferiority & Superiority

HR (95% CI)                             0.91 (0.83, 1.00)

P value (non-inferiority)         < .001
P value (superiority)            0.061

9%
All-Cause Mortality

*Intention-to-Treat Analysis*

HR (95% CI) 0.86 (0.77, 0.97)
P value 0.016

14%
Renal impairment

No dose adjustment is necessary for patients with mild renal impairment (creatinine clearance 50 to 80 ml/min). Clinical experience in patients with moderate renal impairment (creatinine clearance 30 to 50 ml/min) is very limited (see section 5.2). Bydureon is not recommended in these patients.

Bydureon is not recommended for use in patients with end-stage renal disease or severe renal impairment (creatinine clearance < 30 ml/min) (see section 4.4).
NOW APPROVED

BYDUREON® BCise™ (exenatide extended-release) injectable suspension

Coming soon*: a new once-weekly GLP-1 receptor agonist in a new, easy-to-use device.†

Register here to be notified when BYDUREON BCise is available.
V. ΝΤΟΥΛΑΓΛΟΥΤΙΔΗ (TRULICITY®)
# Dulaglutide Clinical Program: HbA1c Change From Baseline at Primary Endpoint

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration</th>
<th>Baseline HbA1c (%)</th>
<th>Comparator</th>
<th>HbA1c Change From Baseline (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AWARD-3</td>
<td>26 weeks</td>
<td>7.6</td>
<td>Monotherapy</td>
<td>-0.71</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Add-on to MET</td>
<td>-0.87</td>
</tr>
<tr>
<td>AWARD-5</td>
<td>52 weeks</td>
<td>8.1</td>
<td>Add-on to MET</td>
<td>-0.39</td>
</tr>
<tr>
<td>AWARD-6</td>
<td>26 weeks</td>
<td>8.1</td>
<td>Add-on to MET+TZD</td>
<td>-0.99</td>
</tr>
<tr>
<td>AWARD-1</td>
<td>26 weeks</td>
<td>8.1</td>
<td>Add-on to MET+SU</td>
<td>-0.46</td>
</tr>
<tr>
<td>AWARD-2</td>
<td>52 weeks</td>
<td>8.1</td>
<td>Combination with insulin lispro +/- MET</td>
<td>-0.63</td>
</tr>
<tr>
<td>AWARD-4</td>
<td>26 weeks</td>
<td>8.5</td>
<td>Combination with insulin lispro +/- MET</td>
<td>-1.41</td>
</tr>
</tbody>
</table>

Data presented are LS means, ITT, LOCF ANCOVA analysis:

Έτοιμη προς χρήση πένα

Η πένα Dulaglutide είναι έτοιμη προς χρήση

- Δεν απαιτείται ανασύσταση ή γέμισμα
- Τοποθετημένη εκ των προτέρων κρυμμένη βελόνα 29-gauge
- Κάθε πένα περιέχει 1 δόση Dulaglutide

Αυτόματη χορήγηση δόσης

- Οι ασθενείς πιέζουν απλά ένα πλήκτρο αντί να τρυπούν μόνοι τους το δέρμα τους με μια βελόνα

99,0% των ασθενών θεωρούν τη χορήγηση εύκολη

- 1. Αφαιρείτε το καπάκι. 2. Τοποθετείτε και απασφαλίζετε. 3. Πιέζετε και κρατάτε.

1. Π.Χ.Π. Trulicity 2016
2. Φ.Ο.Χ. Trulicity 2016
**Κύρια κριτήρια εισαγωγής:**
- Διαβήτης τύπου 2 με HbA1c ≤9,5%
- Ασθενείς που δεν λάμβαναν φάρμακα κατά της υπεργλυκαιμίας ή που αντιμετωπίζονταν με ≤2 OAMs μαζί με ή χωρίς GLP-1 RA ή μόνο με βασική ινσουλίνη
- Ασθενείς ηλικίας ≥50 ετών με εγκατεστημένη καρδιαγγειακή νόσο, ≥55 ετών με υποκλινική αγγειακή νόσο ή ≥60 με ≥2 παράγοντες καρδιαγγειακού κινδύνου

**Κύρια κριτήρια αποκλεισμού:**
- Μη ελεγχόμενος διαβήτης που απαιτεί άμεση θεραπεία
- Βαριά υπογλυκαιμία εντός του προηγούμενου έτους
- Οξύ στεφανιαίο ή αγγειακό εγκεφαλικό επεισόδιο κατά τους τελευταίους 2 μήνες

**Η REWIND ξεκίνησε τον Ιούλιο 2011 και εκτιμάται ότι θα ολοκληρωθεί το 2018**

**Σχεδιασμός για 9622 ασθενείς**

**Κύριο τελικό σημείο:**
- Χρόνος που μεσολαβεί από την τυχαιοποίηση έως την πρώτη εμφάνιση καρδιαγγειακού θανάτου, μη θανατηφόρου εμφράγματος του μυοκαρδίου ή μη θανατηφόρου εγκεφαλικού επεισοδίου (σύνθετη καρδιαγγειακή έκβαση)

**CV = καρδιαγγειακό, GLP-1 RA = αγωνιστής του υποδοχέα του ομοιάζοντος με γλυκαγόνη πεπτιδίου-1, HbA1c = αιμοσφαιρίνη A1c, OAMs = από το στόματος αντιδιαβητικά φάρμακα, REWIND = REsearching cardiovascular Events with a Weekly INcretin in Diabetes.**

VII. ΣΕΜΑΓΛΟΥΤΙΔΗ
Greater weight loss and lower HbA1c levels sustained with semaglutide compared to placebo in the SUSTAIN 6 trial

Lower HbA1c levels maintained for semaglutide throughout the trial period

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Sema 0.5 mg</th>
<th>Sema 1.0 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-104</td>
<td>8.3</td>
<td>7.6*</td>
<td>7.3*</td>
</tr>
</tbody>
</table>

Statistically significantly greater weight loss was sustained with semaglutide

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Sema 0.5 mg</th>
<th>Sema 1.0 mg</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-104</td>
<td>-0.6</td>
<td>-3.6*</td>
<td>-4.9*</td>
</tr>
</tbody>
</table>

Sema: Semaglutide

* p-value is <0.0001 for both semaglutide 0.5 mg vs placebo and semaglutide 1.0 mg vs placebo

Semaglutide significantly reduced the risk of major cardiovascular events in the SUSTAIN 6 trial

Semaglutide demonstrated 26% reduction in composite CV outcome compared with placebo

Key results

- Non-inferiority of semaglutide compared to placebo was confirmed for time to first MACE

- Semaglutide reduced the risk of composite cardiovascular outcome, i.e., time from randomisation to first occurrence of CV death, non-fatal MI or non-fatal stroke, by 26% compared to placebo

- The result was consistent across sensitivity analyses

Hazard ratio = 0.74 (95% CI: 0.58; 0.95)

Events: 108 semaglutide; 146 placebo

p < 0.001 for non-inferiority
p = 0.02 for superiority

Note: p-value is two-sided, pooled data reported for both semaglutide and placebo

MACE: Major adverse cardiovascular event; 3-point MACE comprises cardiovascular death, non-fatal myocardial infarction and non-fatal stroke; CI: Confidence Interval

* No adjustment for multiple tests

Semaglutide reduced the risk of nephropathy but increased risk of retinopathy complications vs placebo in SUSTAIN 6

Semaglutide-treated subjects had significantly lower risk of new or worsening nephropathy

Risk of retinopathy complications significantly higher with semaglutide vs placebo

Note: All p-values are two-sided, pooled data reported for both semaglutide and placebo
HR: Hazard ratio; CI: Confidence interval
Η ΘΕΣΗ ΤΩΝ GLP-1 RAs ΣΤΗΝ ΚΛΙΝΙΚΗ ΠΡΑΞΗ
**GLYCEMIC CONTROL ALGORITHM**

**LIFESTYLE THERAPY**
(Including Medically Assisted Weight Loss)

**Entry A1C < 7.5%**
- **MONOTHERAPY***
  - Metformin
  - GLP-1 RA
  - SGLT-2i
  - DPP-4i
  - TZD
  - AGi
  - SU/GLN

**Entry A1C ≥ 7.5%**
- **DUAL THERAPY***
  - GLP-1 RA
  - SGLT-2i
  - DPP-4i
  - TZD
  - Basal Insulin
  - Colesevelam
  - Bromocriptine QR
  - AGi
  - SU/GLN

**Entry A1C > 9.0%**
- **TRIPLE THERAPY***
  - GLP-1 RA
  - SGLT-2i
  - TZD
  - Basal insulin
  - DPP-4i
  - Colesevelam
  - Bromocriptine QR
  - AGi
  - SU/GLN

**SYMPTOMS**
- NO
- YES
  - DUAL Therapy
  - TRIPLE Therapy
  - INSULIN ± Other Agents

**ADD OR INTENSIFY INSULIN**
Refer to Insulin Algorithm

**PROGRESSION OF DISEASE**

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

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In patients with long-standing suboptimally controlled type 2 diabetes and established atherosclerotic cardiovascular disease, **empagliflozin** or **liraglutide** should be considered as they have been shown to reduce cardiovascular and all-cause mortality when added to standard care.

- Level of evidence B
Σε άτομα με ΣΔτ2 όχι καλά ρυθμισμένο, μακρά διάρκεια νόσου και εγκατεστημένη καρδιοαγγειακή νόσο, η χορήγηση εμπαγλιφλοζίνης ή λιραγλουτίδης επιπρόσθετα του προϋπάρχοντος θεραπευτικού σχήματος μειώνει τα καρδιοαγγειακά επεισόδια.
ΣΥΜΠΕΡΑΣΜΑΤΑ
1. ΙΣΧΥΡΗ ΓΛΥΚΑΙΜΙΚΗ ΡΥΘΜΙΣΗ ΧΩΡΙΣ ΥΠΟΓΛΥΚΑΙΜΙΕΣ
2. ΑΠΩΛΕΙΑ ΒΑΡΟΥΣ
3. ↓ ΑΡΤΗΡΙΑΚΗΣ ΠΙΕΣΗΣ
4. ↓ ΚΑΡΔΙΑΓΓΕΙΑΚΩΝ ΣΥΜΒΑΜΑΤΩΝ (LIRA-SEMA)
6. ↓ ΔΙΑΒΗΤΙΚΗΣ ΝΕΦΡΟΠΑΘΕΙΑΣ (LIRA-SEMA)
ΙΝΣΤΙΤΟΥΤΟ ΜΕΛΕΤΗΣ, ΕΡΕΥΝΑΣ & ΕΚΠΑΙΔΕΥΣΗΣ
ΓΙΑ ΤΟ ΣΑΚΧΑΡΩΔΗ ΔΙΑΒΗΤΗ
ΚΑΙ ΤΑ ΜΕΤΑΒΟΛΙΚΑ ΝΟΣΗΜΑΤΑ

8ο Πανελλήνιο Συνέδριο

23 - 25 Μαρτίου
2018
Grand Serai Hotel
Ιωάννινα
2ο Εκπαιδευτικό Σεμινάριο:
Διαταραχές της οξεοβασικής
ισορροπίας & των πλεκτρολυτών
ΑΠΟ ΤΗ ΘΕΩΡΙΑ ΣΤΗΝ ΠΡΑΞΗ

11 - 13 Μαίου 2018

ξενοδοχείο
Grand Serai, Ιωάννινα

ΟΡΓΑΝΩΣΗ:
ΕΤΑΙΡΕΙΑ ΠΑΘΟΛΟΓΙΑΣ
ΒΟΡΕΙΟΔΥΤΙΚΗΣ ΕΛΛΑΔΟΣ

Υπό την αιγίδα των:
• Ελληνικής Εταιρείας
  Αβρασκεληρίσι
• Ελληνικής
  Διαβιταλογικής Εταιρείας
• Ελληνικής
  Νεφρολογικής Εταιρείας
• Εταιρείας Παθολογίας
  Ελλάδος
• Ινστιτούτο Μελετής
  Έρευνας και Εκπαίδευσης,
  Για το Σάκχαρο Διαβήτη
  και τα Μεταβολικά
  Νοσήματα

Περιορισμένος αριθμός. Απαιτείται προεγγραφή.