Diabetes Treatment: GLP-1 Therapy

Seyed Adel Jahed, M.D., Endocrinologist

Gabric Diabetes Education Association
Disclosures

- Seyed Adel Jahed has received honoraria for lectures or as consultant taking part in advisory board meetings from:
  - Novo Nordisk Pars
  - Sanofi
  - Abidi
  - Merck
  - Eli Lilly
  - AstraZeneca
Treatment options in type 2 diabetes

DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; SGLT2i, sodium glucose co-transporter-2 inhibitor
Achievement of the ABC goals has improved, but remains suboptimal among adults with diabetes

Prevalence of meeting ABC goals among adults aged ≥20 years with diagnosed diabetes, NHANES 1988–2010. Estimates are age- and sex-standardised to the 2007–2010 diabetic NHANES population. *p<0.01, estimates are compared with those of 2007–2010. †p<0.05, estimates are compared with those of 2007–2010

ABC, haemoglobin A1c, BP and LDL cholesterol; BP, blood pressure; HbA1c, glycosylated haemoglobin; LDL, low-density lipoprotein; NHANES, National Health and Nutrition Examination Survey

Stark Casagrande S et al. Diabetes Care 2013;36(8):2271-2279
Start with monotherapy unless:

- **A1c** is greater than or equal to 9%, **consider dual therapy**
- **A1c** is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL or patient is markedly symptomatic, **consider combination injectable therapy**

## Monotherapy

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Lifestyle Management</th>
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<tbody>
<tr>
<td><strong>EFFICACY</strong>*</td>
<td>high</td>
</tr>
<tr>
<td><strong>HYPO RISK</strong></td>
<td>low risk</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>neutral/loss</td>
</tr>
<tr>
<td><strong>SIDE EFFECTS</strong></td>
<td>GI/lactic acidosis</td>
</tr>
<tr>
<td><strong>COSTS</strong>*</td>
<td>low</td>
</tr>
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If A1c is not achieved approximately after 3 months of monotherapy, proceed to 2-drug combination (order not meant to denote any specific preference—choice dependent on variety of patient- & disease-specific factors).

## Dual Therapy

<table>
<thead>
<tr>
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<th>Lifestyle Management</th>
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<td><strong>Sulfonlurea</strong></td>
<td><strong>Thiazolidinedione</strong></td>
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<tr>
<td><strong>EFFICACY</strong>*</td>
<td>high</td>
</tr>
<tr>
<td><strong>HYPO RISK</strong></td>
<td>moderate risk</td>
</tr>
<tr>
<td><strong>WEIGHT</strong></td>
<td>gain</td>
</tr>
<tr>
<td><strong>SIDE EFFECTS</strong></td>
<td>hypoglycemia</td>
</tr>
<tr>
<td><strong>COSTS</strong>*</td>
<td>low</td>
</tr>
</tbody>
</table>

If A1c is not achieved approximately after 3 months of dual therapy, proceed to 3-drug combination (order not meant to denote any specific preference-choice dependent on variety of patient- & disease-specific factors).
If A1c is not achieved approximately after 3 months of triple therapy, and patient (1) on oral combination, move to basal insulin or GLP-1 RA, (2) on GLP-1 RA, add basal insulin or (3) on optimally titrated basal insulin, add aGLP-1 RA or meal time insulin. Metformin therapy should be maintained, while other oral agents may be discontinued on an individual basis to avoid unnecessary complex or costly regimens. (i.e. adding fourth antihyperglycemic agent).

### ADA recommendations 2017

**Combination Injectable Therapy**

*Fig. 8.1: Antihyperglycemic therapy in type 2 diabetes: general recommendations.* The order in the chart is determined by historical availability and the route of administration, with injectables to the right; it is not meant to denote any specific preference. Potential sequences of antihyperglycemic therapy for patients with type 2 diabetes are displayed, with the usual transition moving vertically from top to bottom (although horizontal movement within therapy stages is also possible, depending on the circumstances). DPP-4-i, DPP-4 inhibitor; fxs, fractures; GI, gastrointestinal; GLP-1 RA, GLP-1 receptor agonist; GU, genitourinary; HF, heart failure; Hypo, hypoglycemia; SGLT2-i, SGLT2 inhibitor; SU, sulfonylurea; TZD, thiazolidinedione.  §Usually a basal insulin (NPH, glargine, detemir, degludec). Adapted with permission from Inzucchi et al 2015

Role of incretin effect in healthy insulin response

- Oral glucose load (50 g)
- IV glucose infusion

The incretin effect is diminished in patients with T2DM

* $p<0.05$, healthy volunteers (n=8)

Glucagon levels are elevated in patients with T$_2$DM

n: T2DM patients=54; Normal subjects=33
T2DM, type 2 diabetes mellitus
Insulin response to GLP-1 in T2DM

Physiological levels of GLP-1\(^1\) (15 mM hyperglycaemic clamp)  
Pharmacological levels of GLP-1\(^2\) (15 mM hyperglycaemic clamp)
Type 2 diabetic alpha-cells are sensitive to the inhibitory action of GLP-1 in a dose-dependent manner.

GLP-1, glucagon-like peptide-1
Hare KJ et al. J Clin Endocrinol Metab 2009;94:4679–4687
The glucagonostatic and insulinotropic effects of GLP-1 contribute equally to its glucose-lowering action

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**Insulinotropic effect**

↑ Peripheral glucose disposal

**Glucagonostatic effect**

↓ Hepatic glucose production

GLP-1 infusion (1.0 pmol/kg/min)

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GLP-1, glucagon-like peptide-1
Hare KJ et al. *Diabetes* 2010;59:1765–1770
Effect of GLP-1 is glucose-dependent

- Effects of 4-hour GLP-1 infusion (1.2 pmol/kg/min) in 10 patients with T2DM

Mean (SE); n=10
*p<0.05
GLP-1, glucagon-like peptide-1; SE, standard error
Nauck M et al. Diabetologia 1993;36:741–744
24-h GLP-1 presence is required for 24-h glucose control

Blood glucose profiles: Before native human GLP-1 treatment
After 7 days’ native human GLP-1 treatment

Larsen J et al. Diabetes Care 2001;24:1416–1421 (n=8)
Food triggers the release of incretin hormones (GLP-1 and GIP) by the intestines into the blood. The body makes DPP-4, an enzyme that rapidly breaks down GLP-1 and GIP.
Incretin-based therapies

GLP-1 receptor agonists
- Human GLP-1 analogues
  - Liraglutide
  - Albiglutide
  - Dulaglutide
- Exendin-based therapies
  - Exenatide OW/BID
  - Lixisenatide

DPP-4 inhibitors
- Saxagliptin
- Linagliptin
- Sitagliptin
- Vildagliptin
- Alogliptin
- Teneligliptin
Summary of mode of action of Incretins

**GLP-1 receptor agonists**
- Subcutaneous injection
- Resist degradation by DPP-4
- Active GLP-1 level \(~80\) pmol/L
- High pharmacological level of GLP-1 receptor activity

**DPP-4 inhibitors**
- Oral ingestion
- Inhibit DPP-4 enzyme
- Active GLP-1 level \(~20\) pmol/L
- Increased physiological activity of GLP-1 receptor (mainly after meals)

Physiology vs. Pharmacology: Extra-glycaemic benefits of incretin therapy

GLP-1 effects

- Increasing plasma GLP-1 concentrations
  - ↑ Gastric emptying
  - ↓ Insulin
  - ↓ Glucagon
  - = ↓ Plasma glucose

GLP-1 effects

- ↓ Appetite
- ↓ Food intake
- = Weight loss

Increasing plasma GLP-1 concentrations

Pharmacological GLP-1 levels

Pharmacological GLP-1 levels

Physiological GLP-1 levels

GLP-1RAs

DPP-4is

DPP-4is, dipeptidyl peptidase-4 inhibitors; GLP-1, glucagon-like peptide 1; GLP-1RAs, glucagon-like peptide 1 receptor agonists

Adapted from Holst et al.1

GLP-1RA direct effects on human physiology

Pancreas
- Insulin secretion\(^2,3\) (glucose-dependent) and beta-cell sensitivity
- Insulin synthesis\(^4\)
- Glucagon secretion\(^3\) (glucose-dependent)

Brain
- Body weight\(^5-7\):
  - Satiety
  - Energy intake

Cardiovascular system
- Systolic blood pressure\(^8\)

Liver
- Hepatic glucose output\(^4\)

GLP-1 RA targets six out of eight core defects of T\(_2\)DM

GLP-1RAs have desirable effects beyond glycaemic control

CV FUNCTION

WEIGHT LOSS

GLYCAEMIC CONTROL

Myocardial function and survival in animal models\(^1,2\)

Improved biomarkers of cardiovascular risk\(^1,2\)

Systolic blood pressure\(^1\)

Delayed gastric emptying\(^1,2\)

Fullness and satiety\(^1,2\)

Food intake\(^1,2\)

Insulin secretion\(^1,2\)

Insulin biosynthesis\(^1,2\)

Beta-cell glucose sensitivity\(^2\)

Glucagon secretion\(^2\)

CV, cardiovascular; GLP-1RA, glucagon-like peptide-1 receptor agonist; T2DM, type 2 diabetes mellitus

Native GLP-1 has limited clinical value because of its short half-life

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1
Liraglutide is a once-daily analogue of human GLP-1

Improves pharmacokinetics:
- Albumin binding
- Self-association

- Slow absorption from subcutis
- Stable against DPP-4
- Long plasma half-life ($t_{1/2} \approx 13$ hrs)

DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1
To improve gastrointestinal tolerability, the starting posology is 0.6 mg liraglutide daily.

*Some patients are expected to benefit from an increase in dose from 1.2 to 1.8 mg and, based on clinical response, after at least 1 week, the dose can be increased to 1.8 mg to further improve glycaemic control. Daily doses higher than 1.8 mg are not recommended.

1. Novo Nordisk. Liraglutide SPC. July 2011
The Liraglutide clinical development programme: the continuum of T2DM care

- **Diet/exercise**
- **Start an oral agent**
- **Add another oral agent**
- **Add a third oral or start insulin**

**Liraglutide monotherapy vs. SU**
- LEAD-3

**Liraglutide + met vs. SU + met**
- LEAD-2

**Liraglutide + SU vs. TZD + SU**
- LEAD-1

**Liraglutide + met vs. liraglutide + met + IDet**
- LIRA-DETEMIR

**Liraglutide + met + TZD vs. met + TZD**
- LEAD-4

**Liraglutide + met + SU vs. glargine + met + SU**
- LEAD-5

**Liraglutide + met and/or SU vs. exenatide + met and/or SU**
- LEAD-6

**Liraglutide vs. sitagliptin**
- LIRA-DPP-4

**IDet, insulin detemir; met, metformin; SU, sulphonylurea; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione**

Liraglutide Clinical Development

Completed

- LEAD-1 (n=1041) vs TZD or placebo Add-on to SU
- LEAD-2 (n=1091) vs SU or placebo Add-on to met
- LEAD-4 (n=533) vs placebo Add-on to met + TZD
- LEAD-3 (n=746) vs SU
- LEAD-5 (n=581) vs insulin glargine or placebo Add-on to met + SU
- LIRA-ADD2BASAL™ (n=446) vs placebo Add-on to basal insulin ± met
- LIRA-DETEMIR (n=323) vs liraglutide plus IDet Add-on to met
- LEAD-6 (n=564) vs exenatide BID Add-on to met ± SU
- LIRA-ADD2OD JAPAN™ (n=363) vs 2 OADs Add-on to OAD monotherapy
- LIRA-PRIME JAPAN™ (n=2000) vs OADs as Add-on to met

Ongoing

- LIRA-DPP-4 CHINA™ (n=366) vs sitagliptin Add-on to met
- LIRA-SWITCH™ (n=396) vs sitagliptin Add-on to met, switch from sitagliptin
- LIRA-LIXI™ (n=400) vs lixisenatide Add-on to met
- LIRA-DPP-4 (n=665) vs sitagliptin Add-on to met
- LIBRA (n=51) vs placebo Beta Cell Function
- LEADER® (cardiovascular outcomes trial) SOC plus liraglutide 0.6 mg–1.8 mg vs SOC plus placebo (n=9,340) Drug-naïve or add-on to ≥1 OAD or add-on to basal or premix insulin (alone or in combination with OADs)

Source: ClinicalTrials.gov

Drug naïve | ≥1 OAD | Insulin users | Incretins | Special populations

BID, twice daily; H2H, head-to-head; Lira, liraglutide; Met, metformin; OAD, oral antidiabetes drug; SU, sulphonylurea; TZD, thiazolidinedione

LEADER (cardiovascular outcomes trial) SOC plus liraglutide 0.6 mg–1.8 mg vs SOC plus placebo (n=9,340)
Drug-naïve or add-on to ≥1 OAD or add-on to basal or premix insulin (alone or in combination with OADs)

NN2211-4174 (Japanese patients; n=470) Lira 1.8 mg vs Lira 0.9 mg Add-on to OAD

Ellipse™ (pediatric; n=150) vs placebo Add-on to met ± basal insulin

LIRA-RENAL™ (n=279) vs placebo Add-on to SOC

LIRA-ADD2INSULIN JAPAN™ (n=257) vs placebo Add-on to insulin

LIRA-ADD2OAD JAPAN™ (n=363) vs 2 OADs Add-on to OAD monotherapy

LIRA-Ramadan™ (n=320) vs SU
Add-on to met ± SU

LIRA-ADDEMPER® (Japanese patients; n=470) Lira 1.8 mg vs Lira 0.9 mg Add-on to OAD

LIRA-DETEMIR (n=323) vs liraglutide plus IDet Add-on to met

LIRA-ADD2BASAL™ (n=446) vs placebo Add-on to basal insulin ± met

LIRA-LIXI™ (n=400) vs lixisenatide Add-on to met
Δ HbA$_{1c}$ in the LEAD programme

<table>
<thead>
<tr>
<th>Monotherapy</th>
<th>MET add-on</th>
<th>SU add-on</th>
<th>MET + TZD add-on</th>
<th>MET + SU add-on</th>
<th>MET ± SU add-on</th>
<th>MET add-on</th>
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<tbody>
<tr>
<td>LEAD-3</td>
<td>LEAD-2</td>
<td>LEAD-1</td>
<td>LEAD-4</td>
<td>LEAD-5</td>
<td>LEAD-6</td>
<td>LIRA–DPP-4</td>
</tr>
<tr>
<td>Baseline HbA$_{1c}$ (%)</td>
<td>8.4</td>
<td>8.6</td>
<td>8.6</td>
<td>8.4</td>
<td>8.2</td>
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<thead>
<tr>
<th></th>
<th>Liraglutide 1.2 mg</th>
<th>Liraglutide 1.8 mg</th>
<th>Glimepiride</th>
<th>Glargine</th>
<th>Placebo</th>
<th>Sitagliptin</th>
<th>Exenatide</th>
<th>Placebo</th>
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<td>LEAD-3</td>
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<td>LEAD-2</td>
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<tr>
<td>LEAD-1</td>
<td>-1/6</td>
<td>-1/3</td>
<td>-1/5</td>
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<td>LEAD-4</td>
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<td>LEAD-5</td>
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<td>LEAD-6</td>
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<tr>
<td>LIRA–DPP-4</td>
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*Significant vs comparator; change in HbA$_{1c}$ from baseline for overall population (LEAD-4,-5); add-on to diet and exercise failure (LEAD-3); or add-on to previous OAD monotherapy (LEAD-2,-1)

DPP-4, dipeptidyl peptidase-4; HbA$_{1c}$, glycosylated haemoglobin; LIRA, liraglutide; MET, metformin; OAD, oral antidiabetic drug; SU, sulphonylurea; TZD, thiazoladinedione

Δ Weight in the LEAD programme

*Significant vs comparator

DPP-4, dipeptidyl peptidase-4; LIRA, liraglutide; MET, metformin; SU, sulphonylurea; T2DM, type 2 diabetes mellitus; ZD, thiazolinedione

Composite endpoint:
HbA$_{1c}$ <7.0%, no weight gain, no hypoglycaemia

LIRA-DPP-4: Trial design

N = 665

Inclusion criteria

- Type 2 diabetes
- Age 18–80 years
- HbA1c 7.5–10.0%
- BMI ≤45 kg/m²
- Stable metformin ≥1500 mg/day for >3 months

Main study: 26 weeks

- Liraglutide 1.8 mg (n=221)
- Liraglutide 1.2 mg (n=225)
- Sitagliptin 100 mg (n=219)

Extension 1: 26 weeks

- Liraglutide 1.8 mg (n=176)
- Liraglutide 1.2 mg (n=155)
- Sitagliptin 100 mg (n=166)

Extension 2: 26 weeks

- Liraglutide 1.8 mg (n=150)
- Liraglutide 1.2 mg (n=134)
- Sitagliptin 100 mg (n=68)

Trial information

- Randomised
- Open-label
- 11 European countries, Canada and the USA

Primary objective

To compare the efficacy and safety of treatment with liraglutide or sitagliptin for 26 weeks in individuals with type 2 diabetes who did not achieve adequate glycaemic control with metformin

Primary endpoint

Change in HbA1c from baseline to Week 26

Key secondary endpoints

- Proportion of subjects reaching target HbA1c <7% or ≤6.5%
- Fasting plasma glucose
- Body weight
- Overall treatment satisfaction
- Adverse events

BMI, body mass index; HbA1c, glycosylated haemoglobin.
LIRA–DPP-4: Δ HbA$_{1c}$ from baseline to 52 weeks

Estimated treatment difference (ANCOVA): liraglutide 1.2 mg vs sitagliptin -0.40; liraglutide 1.8 mg vs sitagliptin -0.63 (both $p<0.0001$). Data are mean (1.96 SE) from FAS, LOCF.

HbA$_{1c}$, glycosylated haemoglobin.

Data are from the FAS, LOCF
FAS, full analysis set; LOCF, last observation carried forward
LIRA–DPP-4:
Overall treatment satisfaction (DTSQs) – 52 weeks

Lighter bars = baseline values; darker bars = Week 52 LOCF; *p = 0.0346 vs sitagliptin for change from baseline to Week 52
Mean; data are from the PRO analysis set; Satisfaction score ranges from 0 (lowest satisfaction) to 36 (highest satisfaction)
DTSQs, Diabetes Treatment Satisfaction Questionnaire (status)
LIRA-SWITCH: Trial design

N=407

Inclusion criteria
• Type 2 diabetes
• Age ≥ 18 years
• Stable sitagliptin (100 mg/day) + Met (≥ 1500 mg/day or MTD)† for ≥ 90 days
• HbA1c 7.5-9.5%
• BMI ≥ 20 kg/m²

Trial information
• Double-blind, double-dummy, active-controlled
• Stratified by HbA1c (≤ 8.5% and > 8.5%) and Met (< 1500 mg/day and ≥ 1500 mg/day)

Primary objective
To confirm superiority on glycaemic control of switching from sitagliptin (100 mg/day) to liraglutide (1.8 mg/day) versus continued sitagliptin, both + metformin after 26 weeks

Primary endpoint
Change in HbA1c from baseline to Week 26

Key secondary endpoints
• Change in body weight
• Change in FPG
• Subjects meeting HbA1c targets < 7.0% and ≤ 6.5%
• Safety and tolerability

*L1 subject was not exposed to treatment. Subjects randomised to switch received liraglutide subcutaneously starting at 0.6 mg/day, with weekly dose escalations of 0.6 mg/day until the maintenance dose of 1.8 mg/day was reached; †MTD ≥ 1000 mg/day
BMI, body mass index; HbA1c, glycosylated haemoglobin; Met, metformin; MTD, maximum tolerated dose
Bailey TS et al. Presented at ENDO Annual Meeting, Boston, MA, Apr 2 2016. Poster SAT 689
LIRA-SWITCH: Change in HbA$_{1c}$ from 0–26 weeks

ETD $-0.61\%$
95% CI: $-0.82$; $-0.40$
$p < 0.0001$

Group mean estimates (± standard error of the mean) are from mixed model for repeat measurements with treatment, strata, country and baseline value, all nested within visit, and are adjusted according to observed baseline distribution.

CI, confidence interval; ETD, estimated treatment difference; HbA$_{1c}$, glycosylated haemoglobin

Bailey TS et al. Presented at ENDO Annual Meeting, Boston, MA, Apr 2 2016. Poster SAT 689
LIRA-SWITCH:
Change in body weight from 0–26 weeks

Group mean estimates (± standard error of the mean) are from mixed model for repeat measurements with treatment, strata, country and baseline value, all nested within visit, and are adjusted according to observed baseline distribution.

CI, confidence interval; ETD, estimated treatment difference
Bailey TS et al. Presented at ENDO Annual Meeting, Boston, MA, Apr 2 2016. Poster SAT 689
LIRA-SWITCH:
Subjects meeting HbA$_{1c}$ targets at week 26

AACE, American Association of Clinical Endocrinologists; ADA, American Diabetes Association; CI, confidence interval; HbA$_{1c}$, glycosylated haemoglobin; OR, odds ratio

Bailey TS et al. Presented at ENDO Annual Meeting, Boston, MA, Apr 2 2016. Poster SAT 689
**LIRA-RENAL: Study design**

**Trial objective**
To investigate the efficacy and safety of liraglutide vs. placebo as add-on to existing diabetes medication in subjects with T2DM and moderate renal impairment.

**Key inclusion criteria**
- Moderate renal impairment† diagnosed more than 90 days prior to screening
- Stable diabetes treatment for 90 days prior to screening

**Primary endpoint**
- Change in HbA\(_1c\) from baseline to Week 26

**Key secondary endpoints**
- Change from baseline in renal function
- Number of responders to HbA\(_1c\) <7% and no weight gain
- Number of responders to HbA\(_1c\) <7% and no minor or severe hypoglycaemic episodes

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*If HbA\(_1c\) ≤8%, insulin dose was reduced by 20%; †eGFR (MDRD formula) was based on serum creatinine, sex, age, body size and race BMI, body mass index; eGFR, estimated glomerular filtration rate; HbA\(_1c\), glycosylated haemoglobin; MDRD, modification of diet in renal disease; OAD, oral anti-diabetic drug; OD, once daily; RI, renal impairment; SU, sulphonylurea; T2DM, type 2 diabetes mellitus

Primary endpoint: Change in HbA$_{1c}$

Estimated means ± standard error from mixed model for repeated measurements
CI, confidence interval; ETD, estimated treatment difference; HbA$_{1c}$, glycosylated haemoglobin
Change in body weight

Body weight change from baseline to Week 26 (kg)

ETD: -1.32*

95% CI: -2.24; -0.40

p=0.0052

Time since randomisation (weeks)

Body weight (kg)

Liraglutide 1.8 mg

Placebo

Estimated means ± standard error from mixed model for repeated measurements
BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference
LIRA-RENAAL:
Renal parameters – eGFR (MDRD) over 26 weeks

Estimated means from mixed model for log-repeated measurements
BL, baseline; CI, confidence interval; eGFR, estimated glomerular filtration rate; ETR, estimated treatment ratio; MDRD, modification of diet in renal disease

ETR: 0.98
95% CI: 0.94;1.02
p=0.36
Renal parameters: Urinary albumin/creatinine

<table>
<thead>
<tr>
<th>Time since randomisation (weeks)</th>
<th>Mean albumin/creatinine (mg/mmol)</th>
<th>Ratio mean albumin/creatinine</th>
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<tbody>
<tr>
<td>0</td>
<td></td>
<td>6.0</td>
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<tr>
<td>2</td>
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<td>6.5</td>
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<td>9.0</td>
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<tr>
<td>26</td>
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<td>5.5</td>
</tr>
</tbody>
</table>

ETR: 0.83
95% CI 0.62; 1.10
p = 0.1856

CI, confidence interval; ETR, estimated treatment ratio
Scott D et al. ASN 2014; abstract number FR-OR 122

Pre-existing insulin* (± metformin) + liraglutide 1.8 mg

Pre-existing insulin* (± metformin) + placebo

Duration 26 weeks

End of treatment

Randomisation (1:1)

**LIRA-ADD2BASAL: Study design**

**446 patients**

* T2DM  
* HbA₁c 7–10%  
* BMI 20–45 kg/m²  
* Basal insulin analogue therapy

**Trial information**

* Initiation: September 2012  
* Double blinded  
* Patients stratified by screening HbA₁c; OAD treatment; type of basal insulin analogue

**Trial objective**

To investigate the effect of liraglutide vs. placebo when added to basal insulin analogues ± metformin in subjects with T₂DM

**Key inclusion criteria**

Stable insulin detemir or insulin glargine ≥20 U/day for 8 weeks (± metformin ≥1500 mg/day)

**Primary endpoint**

* Change in HbA₁c from baseline to Week 26

**Key secondary endpoints**

* Change in body weight from baseline to Week 26  
* Change in FPG from baseline to Week 26  
* Change in 7-point SMPG profile from baseline to Week 26  
* Number of hypoglycaemic episodes

*Insulin detemir or insulin glargine ≥20 U/day; if HbA₁c ≤8%, insulin dose was reduced by 20%

BMI, body mass index; FPG, fasting plasma glucose; HbA₁c, glycosylated haemoglobin; OAD, oral antidiabetic drug; SMPG, self-measured plasma glucose; T₂DM, type 2 diabetes mellitus; U, units of insulin
LIRA-ADD2BASAL: Δ HbA₁c from baseline to Week 26

- Liraglutide 1.8 mg
  - Change in HbA₁c (%) = -1.30
- Placebo
  - Change in HbA₁c (%) = -0.11

Treatment difference: -1.19%
95% CI: [-1.39; -0.99]

p<0.0001

Estimated means from mixed model for repeated measurements
CI, confidence interval; HbA₁c, glycosylated haemoglobin
Ahmann A et al. Diabetes Obes Metab 2015;17:1056-1064
**LIRA-ADD2BASAL:**
Body weight change over 26 weeks

Body weight estimated mean change from baseline to Week 26

*95% CI: [-3.85; -2.37]  
P<0.0001

CI, confidence interval; ETD, estimated treatment difference
Clinical Trials Data

or

Real World Evidence?
Real world studies confirm HbA$_{1c}$ lowering effects of liraglutide

Baseline (%)

<table>
<thead>
<tr>
<th>Duration (m)</th>
<th>0/0</th>
<th>-1/0</th>
<th>-2/0</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>5948</td>
<td>256</td>
<td>287</td>
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<td>9.4</td>
<td>9.6</td>
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<td>7.3</td>
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</tr>
<tr>
<td>36</td>
<td>6.5</td>
<td>8.7</td>
<td>6.1</td>
</tr>
<tr>
<td>60</td>
<td>6.1</td>
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<td>5.7</td>
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</tbody>
</table>

HbA$_{1c}$ reduction (%)

<table>
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<th>0/0</th>
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</tbody>
</table>

Achievement of glycemic targets in real world studies

Baseline (%) 8.8 8.5 9.1 8.7 8.2 8.4 8.6 7.8 7.9 517 7.8 8.1

Patients achieving HbA1c ≤7.0% (%)

Duration (m) 6 24 12 12 24 12 6 6 12 6 6

N 287 2607 245 481 205 725 395 234 376 517 234 195

Real world studies confirm
body weight lowering effects of liraglutide

Baseline (kg) 0/0

Duration (m) 12 6 3 24 12 12 8 24 9.4 12 6 12 6 24 3 6
N 256 287 193 2029 245 481 130 205 166 725 395 517 933 86 196 195

Body weight reduction (kg)

-3.9 -3.8 -2.4 -3.0 -3.5 -4.1 -4.1 -4.9 -4.6 -3.0 -3.1 -2.6 -3.4 -4.0 -4.0


Δ Weight observed in clinical trials

-1.2 kg -3.0 kg
The last, not the least...

In the era of growing number of diabetes medications and new data, we should consider the below factors to select the proper component for each individual patient:

- Effectiveness
- Safety profiles
- Side effects
- Extra-glycemic effects
- Cardiovascular effects
- Our experience in handling
- Availability
- Patient preference
- Cost
Visit the Novo Nordisk booth to learn how we are changing diabetes.
Thanks for your attention