Safety profile of Liraglutide: Recent Updates

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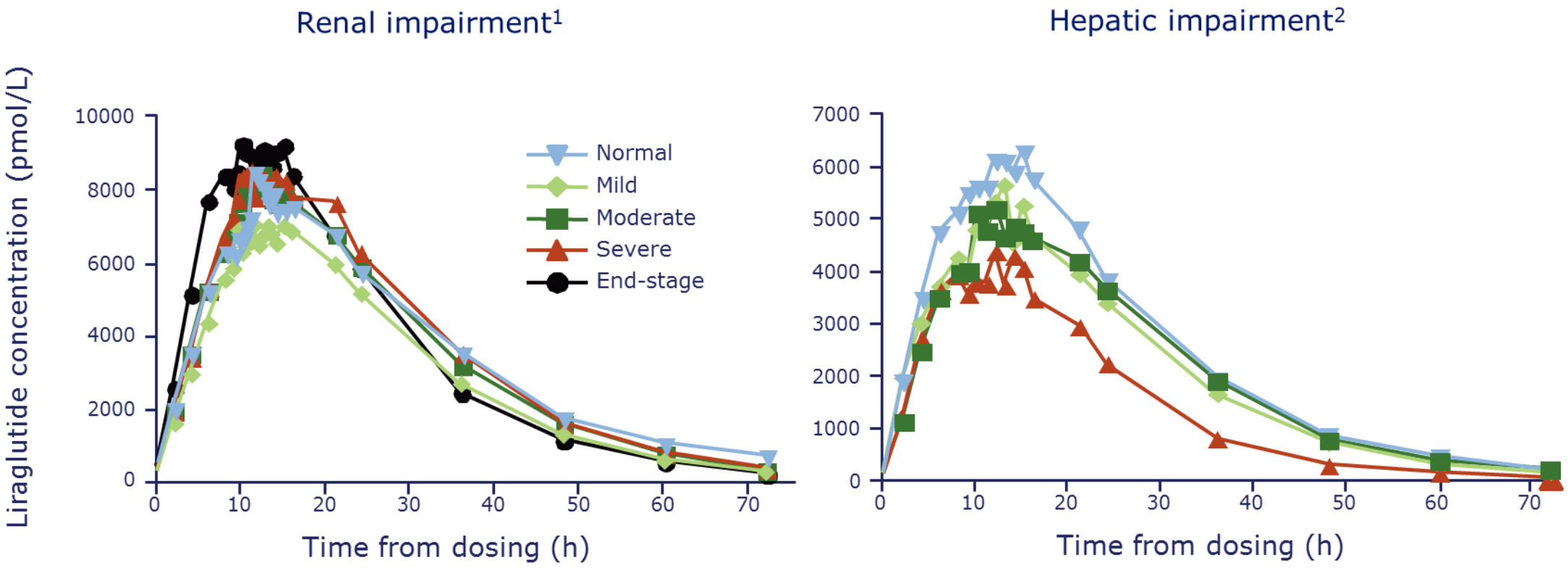
Pancreatitis: Victoza® post-marketing experience: spontaneous reports of pancreatitis

- For the majority of the cases, there is too limited information to ascertain a causal relationship
- In cases with relevant information, the majority had confirmed risk factors (e.g. gallstones, hyperlipidaemia, smoking, past history of pancreatitis, relevant concomitant medications, etc.)
- Overall, the reporting rate is below the background diabetes population

Content overview

- Overall safety
- C-cell safety
- Pancreatitis
- Altered renal function
- Cardiovascular safety
- Conclusion

Renal function: Pharmacokinetics of liraglutide in patients with renal or hepatic impairment unchanged

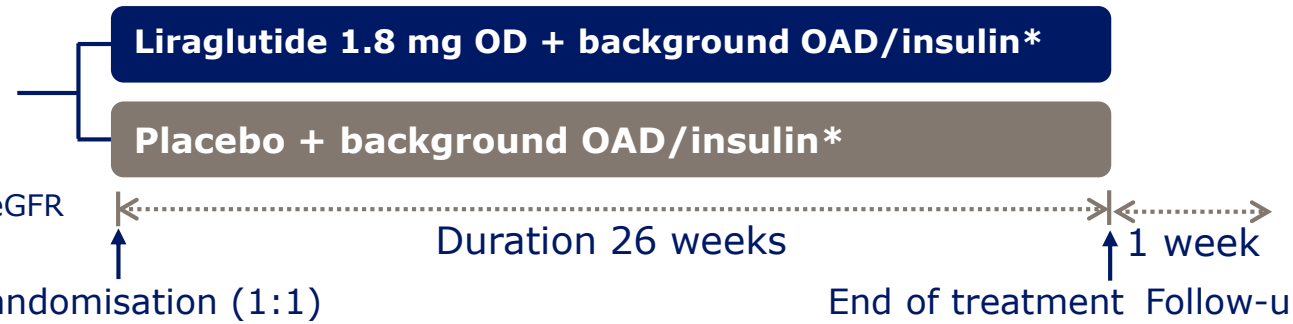


1. Jacobsen *et al. Br J Clin Pharmacol* 2009;68:898–905; 2. Flint *et al. Br J Clin Pharmacol* 2010;70:807–14

LIRA-RENAL: Study design

N = 279

Inclusion criteria
- 18–80 years
- T2DM
- HbA_{1c} 7–10%
- BMI 25–45 kg/m^2
- Moderate renal impairment (eGFR 30–59 mL/min/1.73m^2)†



Trial information
- Initiation: June 2012
- Subjects stratified by renal function and insulin treatment
- Double-blinded, placebo-controlled, randomised, multicentre, multinational

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

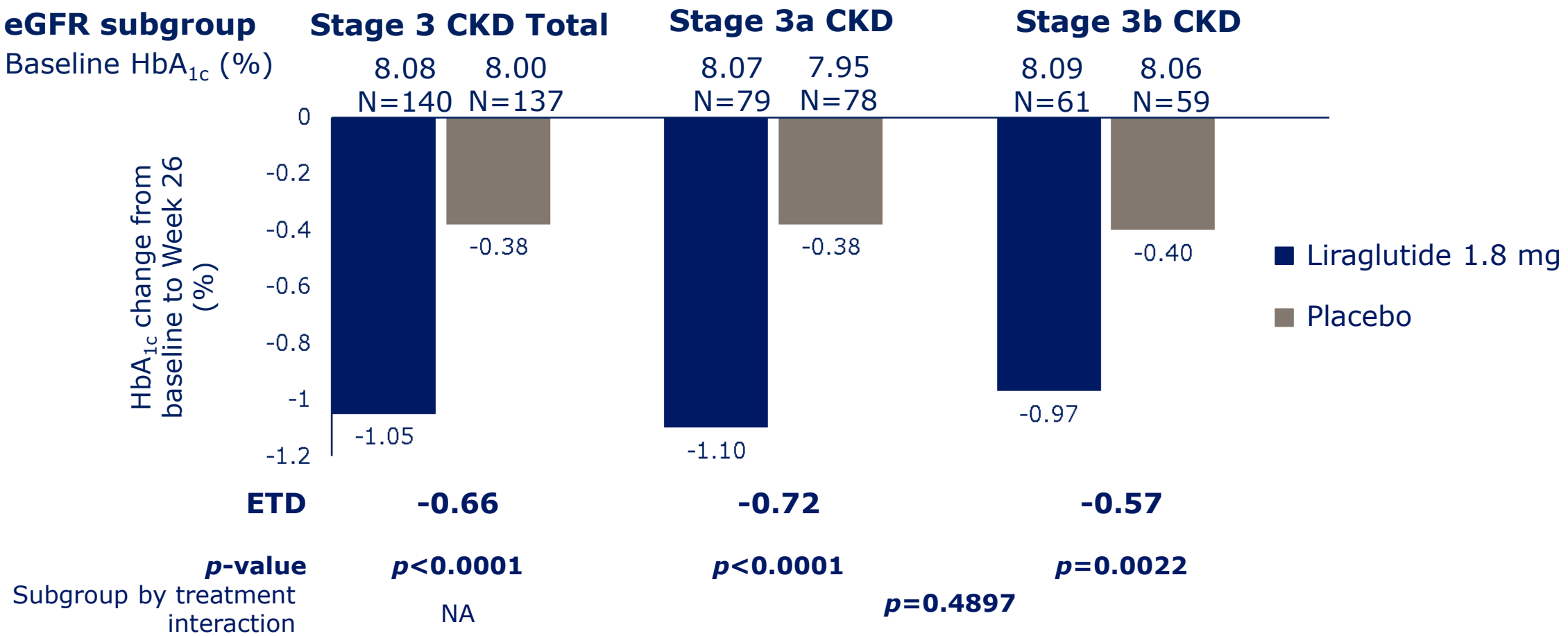
Key secondary endpoints
- Change from baseline in renal function
- Number of responders to HbA_{1c} <7.0% and no minor or severe hypoglycaemic episodes
- Change from baseline in FPG

*If HbA_{1c} ≤8%, insulin dose was reduced by 20%. Liraglutide or placebo was initiated at a starting dose of 0.6 mg/day, with subsequent weekly dose escalations of 0.6 mg/day until the maintenance dose of 1.8 mg/day was reached. At the discretion of the investigator, the dose escalation could be extended up to 4 weeks in case of GI adverse events; †eGFR (MDRD formula) was based on serum creatinine, sex, age, body size and race

BMI, body mass index; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; GI< gastrointestinal; HbA_{1c}, glycosylated haemoglobin; MDRD, modification of diet in renal disease; OAD, oral antidiabetic drug; OD, once daily; SU, sulphonylurea; T2DM, type 2 diabetes mellitus

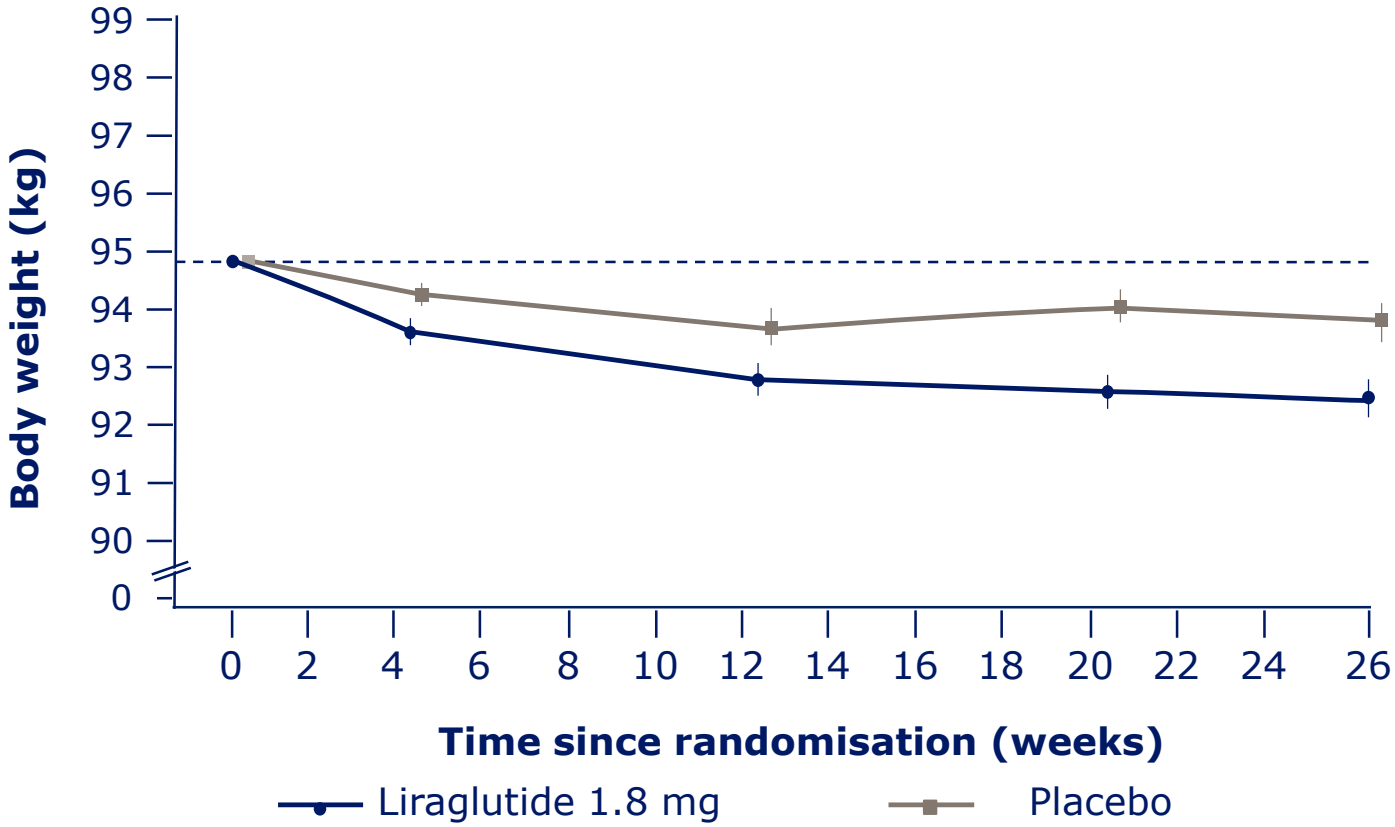
Trial ID:NN2211-3916. Available at http://clinicaltrials.gov/ct2/show/NCT01620489. Last accessed May 2016

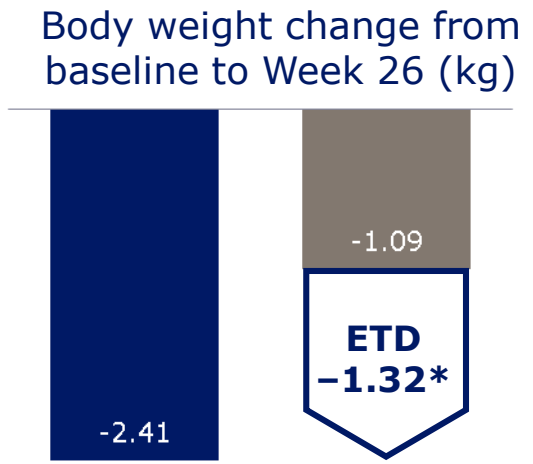
LIRA Renal : Results: HbA_{1c} by baseline renal function



CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate; HbA_{1c}, glycosylated haemoglobin
Davies MJ et al. *Diabetes Care* 2016;39:222-30.

LIRA Renal: Results: Change in body weight



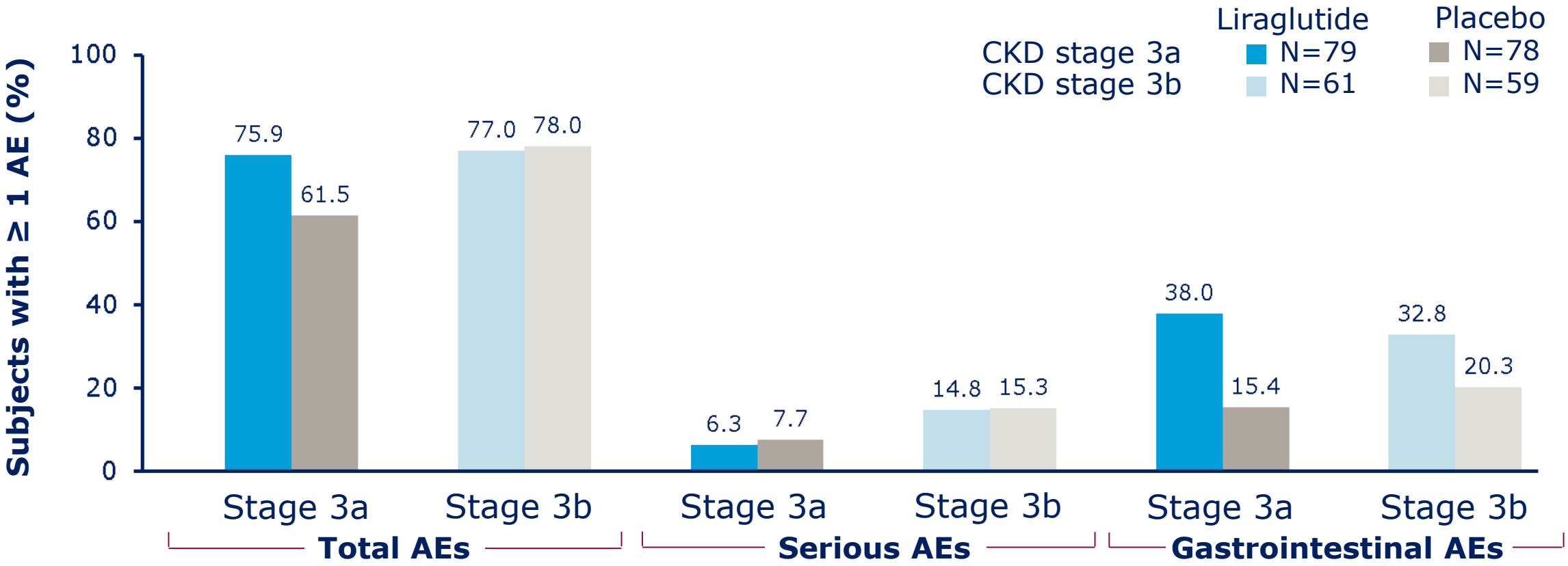


p=0.0052

*95% CI: –2.24; –0.40

Estimated means ± standard error from mixed model for repeated measurements
BMI, body mass index; CI, confidence interval; ETD, estimated treatment difference
Davies MJ et al. *Diabetes Care* 2016;39:222-30.

LIRA Renal: Safety overview by baseline renal function



There was no significant difference in the proportion of subjects suffering from adverse events between the eGFR subgroups

AE, adverse events; CKD, chronic kidney disease; eGFR, estimated glomerular filtration rate

Davies MJ et al. *Diabetes Care* 2016;39:222-30.

Renal Function :Summary

- Liraglutide resulted in superior glycaemic control and weight loss vs placebo
  - No differences were observed between the eGFR subgroups
- Liraglutide did not affect renal function
- No unexpected safety or tolerability issues were observed for liraglutide
  - A higher rate of gastrointestinal side-effects was reported with liraglutide compared with placebo
  - No significant differences were observed between the eGFR subgroups
  - Five deaths occurred in the trial (4 with liraglutide and 1 with placebo)
    - Assessed as unlikely to be related to liraglutide use
- Liraglutide was associated with low rates of hypoglycaemia

eGFR, estimated glomerular filtration rate

Davies MJ et al. *Diabetes Care* 2016;39:222-30.

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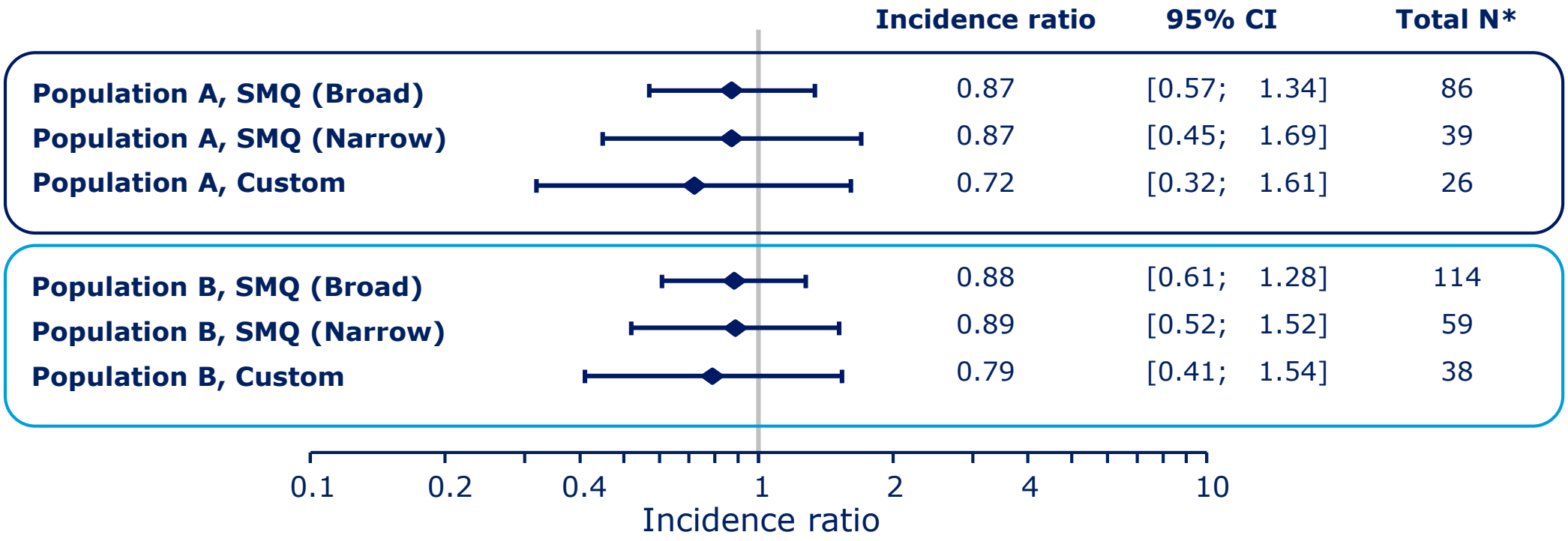
Cardiovascular safety : Meta-analysis of MACE in liraglutide phase 3 trials : Established safety



*Number of subjects with MACE: liraglutide + total comparator.
CI: confidence interval; MACE: major adverse cardiovascular event; N: number; SMQ: standardised MedDRA query.
Marso et al. Presented at American Heart Association Scientific Sessions, Chicago, 13–17 November 2010; Marso et al. *Diab Vasc Dis Res* 2011; 8:237-40.

LEADER: Cardiovascular Outcome Trial with Liraglutide

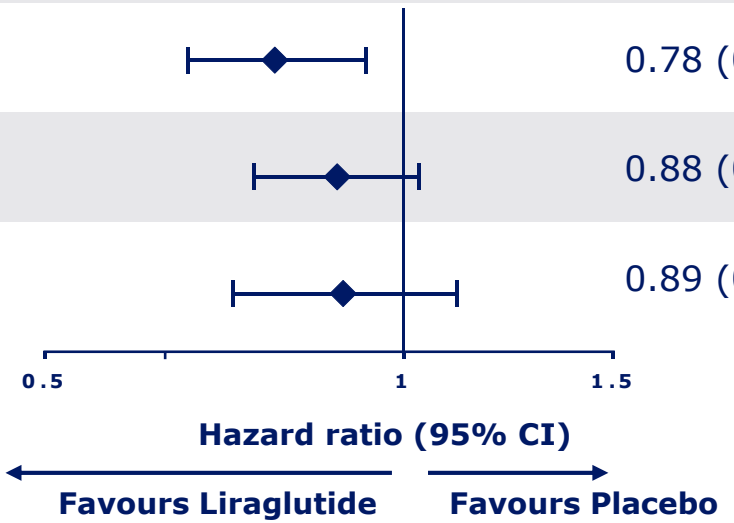
company announcement

Victoza® significantly reduces the risk of major adverse cardiovascular events in the LEADER trial

Bagsværd, Denmark, 4 March 2016 - Novo Nordisk today announced the top-line results from the LEADER trial, which investigated the cardiovascular safety of Victoza® (liraglutide) over a period of up to 5 years in more than 9,000 adults with type 2 diabetes at high risk of major adverse cardiovascular events. The trial compared the addition of either Victoza® or placebo to standard of care and met the primary endpoint of showing non-inferiority as well as demonstrating superiority, with a statistically significant reduction in cardiovascular risk. The primary endpoint of the study was defined as the composite outcome of the first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke. The superior reduction of major adverse cardiovascular events demonstrated by Victoza® was derived from all three components of the endpoint.

LEADER Trial: key results documenting Cardiovascular safety

	Hazard ratio (95% CI)	p-value	Liraglutide N	Liraglutide %	Liraglutide R	Placebo N	Placebo %	Placebo R
Number of patients			**4668**	**100.0**		**4672**	**100.0**	
CV death	0.78 (0.66 ; 0.93)	0.007	219	4.7	1.2	278	6.0	1.6
Non-fatal MI	0.88 (0.75 ; 1.03)	0.11	281	6.0	1.6	317	6.8	1.8
Non-fatal stroke	0.89 (0.72 ; 1.11)	0.30	159	3.4	0.9	177	3.8	1.0



Hazard ratios and p-values were estimated with the use of a Cox proportional-hazards model with treatment as a covariate.
%, percentage of group; CI, confidence interval; CV, cardiovascular; HR, hazard ratio; N, number of patients; R, incidence rate per 100 patient-years of observation.
Marso SP et al. *N Engl J Med* 2016. DOI: 10.1056/NEJMoa1603827.

Overall Summary

- Liraglutide alone, or in combination with OADs, provides effective glycaemic control with a low risk of hypoglycaemia with an overall favourable safety profile.
- Long term data does not show increase in calcitonin levels compared to any active comparators.
- Liraglutide may not be the preferred agent in patients with acute pancreatitis or with a past history of pancreatitis.
- Safety and efficacy of Liraglutide has been demonstrated in patients with renal dysfunction and can be used in patients with eGFR>30 ml/min/1.7 $m^{2.}$
- Meta analysis of the clinical data and the LEADER trial have demonstrated Cardiovascular safety with Liraglutide.

Abbreviated prescribing information

Presentation: Prefilled, disposable pen containing 18 mg of liraglutide in 3 mL of solution.
Indications: Victoza® is indicated for treatment of adults with type 2 diabetes to achieve glycaemic control in monotherapy and in combination with oral glucose-lowering medicinal products and/or basal insulin when these, together with diet and exercise, do not provide adequate glycaemic control.
Dosage and administration: The starting dose is 0.6 mg once daily. After at least one week, the dose should be increased to 1.2 mg. Based on clinical response and after at least one week, the dose can be increased to 1.8 mg to further improve glycaemic control. Victoza® can currently not be recommended for use in patients with severe renal impairment or hepatic impairment. Victoza® is administered once daily at any time, independent of meals, and can be injected subcutaneously in the abdomen, thigh, or upper arm. Victoza® should not be administered intravenously or intramuscularly. In combination with metformin with or without a thiazolidinedione, no dose adjustment is required. When Victoza® is added to sulphonylurea therapy, a reduction in the dose of sulphonylurea should be considered to reduce the risk of hypoglycaemia.
Contraindications: Hypersensitivity to the active substance or any of the excipients.
Special warnings and precautions: Victoza® should not be used in patients with type 1 diabetes mellitus or for the treatment of diabetic ketoacidosis. Victoza® is not a substitute for insulin. Due to limited experience, Victoza® is not recommended in patients with inflammatory bowel disease or diabetic gastroparesis. There is limited experience in patients with congestive heart failure New York Heart Association (NYHA) class I-II and no experience in patients with NYHA class III-IV. Use of GLP-1 analogues has been associated with the risk of pancreatitis. Patients should be informed of the characteristic symptom of acute pancreatitis: persistent, severe abdominal pain. If pancreatitis is suspected, discontinuation of medicinal products should be considered. Thyroid adverse events, including increased blood calcitonin, goitre, and thyroid neoplasm, were reported in clinical trials, particularly in patients with preexisting thyroid disease. Patients treated with Victoza® should be advised of the potential risk of dehydration in relation to gastrointestinal side effects and take precautions to avoid fluid depletion.
Pregnancy and lactation: Victoza® should not be used in women who are pregnant, who wish to become pregnant, or who are breastfeeding.
Undesirable effects: The most frequently reported adverse reactions in patients treated with Victoza® are nausea and diarrhoea. Less common adverse reactions include headache, vomiting, dyspepsia, abdominal pain upper, constipation, gastritis, flatulence, abdominal distension, gastroesophageal reflux disease, bronchitis, nasopharyngitis, dizziness, fatigue, anorexia, decreased appetite, injection site reactions, abdominal discomfort, toothache, rash, increased heart rate, and hypoglycaemia. Since the market introduction of Victoza®, allergic reactions and dehydration (sometimes with a decrease in kidney function) have been reported. Patients receiving Victoza® in combination with a sulphonylurea may have an increased risk of hypoglycaemia. The risk can be lowered by a reduction in the dose of sulphonylurea. Few cases (less than 0.2%) of acute pancreatitis have been reported during long-term clinical trials with Victoza®. Pancreatitis was also reported post-marketing.
Overdose: From clinical trials and marketed use overdoses have been reported up to 40 times (72 mg) the recommended maintenance dose. Events reported included severe nausea and severe vomiting. None of the reports included severe hypoglycaemia. All patients recovered without complications.
IRC: 1228226670 **Date of preparation:** Locally Approved Labeling in Iran Version (STF Q4 2014)