ELIXA: Lixisenatide LYXUMIA, ADLYXYN CV Outcomes Trial Summary

Lixisenatide: Cardiovascular (CV) Outcomes and Mortality in Patients with Type 2 Diabetes Mellitus (T2DM) and Acute Coronary Syndrome (ACS)

In patients with T2DM and recent ACS, does lixisenatide reduce CV risk compared to placebo when added to standard care?

**BOTTOM LINE**

**Lixisenatide versus placebo plus standard care:** not too bad but nothing really good either. (Note – currently not available in Canada)

- Neutral CV results. Achieved non-inferiority, but no indication of any particular CV outcome benefit.
- Serious adverse events (SAE) similar to placebo (plus standard care): specifically: pancreatitis, pancreatic neoplasms, or allergic reactions.
- Adverse events leading to discontinuation was higher with lixisenatide vs. placebo (plus standard care) (NNH=24/2.1 YEARS).
- Neutral CV results with ELIXA and TECOS trials somewhat disappointing given recent trials with positive CV results (i.e, LEADER, EMPA-REG, SUSTAIN-6) (see related RxFiles Trial Summaries & Outcome Comparison Chart).
- Reasonably safe choice for patients who cannot take a recommended second-line diabetes agent; however, compared to placebo + standard care, for every 28 patients on lixisenatide for 2.1 years, 1 additional patient will discontinue the drug due to a GI adverse event.

**BACKGROUND**

- Lixisenatide (LYXUMIA) is a glucagon-like peptide 1 receptor agonist (GLP-1) approved in the European Union in 2013 for use in patients with T2DM as an add-on to metformin, pioglitazone, SU and/or basal insulin. Approved by the FDA July 2016.
- Non-inferior outcome trial mandated by the FDA to ensure CV safety in the “post-rosiglitazone era”.

**TRIAL BACKGROUND**

**DESIGN:** Randomized, double-blind, placebo-controlled, international (49 countries) multi-centre trial with a 1 week run-in phase. Non-inferiority analysis (PP population) for primary efficacy outcome followed by superiority analysis (ITT population). Funding: Sanofi (LYXUMIA manufacturer). Enrolment/ follow-up period: 2010–2015.

**INTERVENTION: Lixisenatide 20mcg subcut vs. placebo, added to existing therapy.**
- Patients were randomized to lixisenatide 10 mcg subcut daily which was increased after 2 weeks to a maximum of 20 mcg at investigators’ discretion.

**EXCLUSION:** Age <30 yrs, PCI within previous 15 days, CABG following qualifying ACS event, planned coronary revascularization ≤90d after screening, eGFR<30ml/min/1.73m², HbA1c<5.5% or >11%, irritable bowel disease, history of medullary thyroid cancer, unexplained pancreatitis or chronic pancreatitis.

**POPULATION** at baseline: n= 6068, age 60 ± 9.7 yrs, ~69% male, eGFR 76 ± 21(mL/min/1.73m²), LDL 2.03± 0.9 mmol/L, SBP 130 ± 17 mmHg; North America 13.3%, Eastern Europe 26%, South or Central America 32%; **Caucasian** ~75%, **Asian** ~12.7%, African-American/Black ~3.7%

**CV comorbidity/risk factors:** MI 22%, PCI 67%, CABG 8.4%, HTN 76%, stroke 5%, PAD 7%, HF 22%, HbA1c 7.7% ± 1.3; current smoker 11.7%, BMI 30.1 ± 5.7 kg/m²; **Weight:** ~85 ± 19.4 kg; T2DM **duration** 9.3 ± 8.2 yrs

**Qualifying ACS event:** NSTEMI 39%, STEMI 44%, unstable angina 17.2%, unclassified 0.2%

**Medications:** metformin 66.3%, insulin 39.1%, SU 33%, TZD 1.6%, **ACEI/ARB** 85%, **BB 84%, statin 93%, antiplatelet 97.5%**

**RESULTS**

**Follow-up: median 2.1 year**

**TABLE 1: EFFICACY & SAFETY NON-INFERIORITY DATA (NNT/NHI = number needed to Treat for Benefit / Harm)**

<table>
<thead>
<tr>
<th>PRIMARY ENDPOINT</th>
<th>CLINICAL ENDPOINTS ITT ANALYSIS</th>
<th>LIXISENATIDE (20MCOS) n=3034</th>
<th>PLACEBO n=3034</th>
<th>HR (95% CI)</th>
<th>P VALUE</th>
<th>ARR/ARI</th>
<th>NNT/NHI /25 MON.</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, non-fatal MI, non-fatal stroke or unstable angina (first event)</td>
<td>13.4% (n=406) 13.2% (n=399)</td>
<td>1.02 (0.89-1.17)</td>
<td>P&lt;0.001 (non-inferiority) 0.81 (superiority)</td>
<td>0.63</td>
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<tr>
<td>CV death (all events)</td>
<td>5.1% (n=156)</td>
<td>5.2% (n=158)</td>
<td>0.98 (0.78-1.22)</td>
<td>0.85</td>
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<tr>
<td>MI (all events)</td>
<td>8.9% (n=270)</td>
<td>8.6% (n=261)</td>
<td>1.03 (0.87-1.22)</td>
<td>0.71</td>
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<table>
<thead>
<tr>
<th>SECONDARY ENDPOINTS</th>
<th>CLINICAL ENDPOINTS</th>
<th>LIXISENATIDE (20MCOS) n=3034</th>
<th>PLACEBO n=3034</th>
<th>HR (95% CI)</th>
<th>P VALUE</th>
<th>ARR/ARI</th>
<th>NNT/NHI /25 MON.</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st endpoint or hospitalization for HF</td>
<td>15% (n=456)</td>
<td>15.5% (n=460)</td>
<td>0.97 (0.85-1.10)</td>
<td>0.63</td>
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</tr>
<tr>
<td>1st endpoint, hospitalization for HF or revascularization</td>
<td>21.8% (n=661)</td>
<td>21.7% (n=659)</td>
<td>1.00 (0.90-1.11)</td>
<td>0.96</td>
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</tr>
<tr>
<td>Hospitalization for HF -with no prior HF</td>
<td>4% (n=122)</td>
<td>4.2% (n=127)</td>
<td>0.96 (0.75-1.23)</td>
<td>0.75</td>
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<tr>
<td>-with prior HF</td>
<td>2.4% (n=56/2352)</td>
<td>2.5% (58/2358)</td>
<td>0.97 (0.67-1.40)</td>
<td>0.87 for interaction</td>
<td></td>
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<tr>
<td>Death from any cause</td>
<td>7% (n=211)</td>
<td>7.4% (n=233)</td>
<td>0.94 (0.78-1.13)</td>
<td>0.5</td>
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| HBa1c | by 0.27% (-0.31 to -0.22%) |
| Systolic BP | by 0.8 mmHg (-1.3 to -0.3 mmHg) |
| Weight | by 0.7 kg (-0.5 to -0.5 kg) |
| 85.5% in lixisenatide group took max dose, 96.5% in placebo took volume matched max dose at end of the study |

**TABLE 2: ADVERSE EVENTS (NNT/H = number needed to Treat for Benefit / Harm)**

<table>
<thead>
<tr>
<th>CLINICAL ENDPOINTS</th>
<th>LIXISENATIDE (n=3034)</th>
<th>PLACEBO (n=3034)</th>
<th>P VALUE</th>
<th>ARR/ARI (POOLED)</th>
<th>NNT/NHI /25 MON.</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse events leading to discontinuation</td>
<td>11.4% (n=347)</td>
<td>7.2% (n=217)</td>
<td>&lt;0.001</td>
<td>4.2%</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td>Gl event leading to discontinuation</td>
<td>4.9% (n=149)</td>
<td>1.2% (n=37)</td>
<td>&lt;0.001</td>
<td>3.7%</td>
<td>28</td>
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<tr>
<td>Nausea</td>
<td>3% (n=91)</td>
<td>0.4% (n=11)</td>
<td>&lt;0.001</td>
<td>2.6%</td>
<td>39</td>
<td></td>
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<tr>
<td>Vomiting</td>
<td>1.1% (n=33)</td>
<td>0.2% (n=5)</td>
<td>&lt;0.001</td>
<td>0.9%</td>
<td>112</td>
<td></td>
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<tr>
<td>Serious adverse events (SAE)</td>
<td>20.6% (n=625)</td>
<td>22.1% (n=669)</td>
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<tr>
<td>Hypoglycaemia events</td>
<td>16.6% (n=504)</td>
<td>15.2% (n=462)</td>
<td>p=0.14</td>
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<td></td>
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<tr>
<td>Urine albumin/creatinine ratio</td>
<td>+26%</td>
<td>+32%</td>
<td>0.07</td>
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- similar rates of SAEs, severe hypoglycaemia, pancreatitis, pancreatic neoplasms, or allergic reactions compared to placebo.
- pancreatitis: 5 pts in lixisenatide vs. 8 pts in placebo group.
- pancreatic cancer: 3 pts in lixisenatide vs. 9 pts in placebo group.
- allergic reaction: 27 pts in lixisenatide vs. 25 pts in placebo group.
STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS:
- First published GLP1-A CV outcome trial.
- Well-designed RCT (properly randomized [allocation concealment, balanced baseline demographics]; registered; appropriately powered; all CV outcomes were pre-specified & clinically relevant; independent, blinded adjudication of CV, pancreatic, and allergic events).
- 96.3% in treatment group and 96.1% in placebo group completed study (among those who did not die); vital status not confirmed for ~1% of patients.
- ITT and PP analyses were performed for primary endpoints. Sensitivity analysis (e.g., adjustment for eGFR, HbA1c, and history of stroke; exclusion of CV events occurring more than 30 days after drug discontinuation) did not result in statistically significant changes.
- Primary composite endpoint consistent (homogeneous) among subgroups.
- Serious hypoglycemic episodes requiring intervention by another person was lower in lixisenatide group (14 patients reporting 16 events) than placebo group (24 patients reporting 37 events).

LIMITATIONS:
- Study medication was discontinued in 27.5% in treatment and 24% in placebo group (P=0.002); GI AE was the most common reason for discontinuation.
- Short trial duration (2.1 years).
- No adjustments made for multiplicity of exploratory outcomes (risk of false-positive result [type 1 error]).
- Non-inferiority margin of 1.3 was arbitrarily set by the FDA, and thus may not represent a minimally-clinically important difference to clinicians or patients.

UNCERTAINTIES:
- Applicability of results to patients without established CVD or with more complicated coexisting illnesses.
- Lack of real-world data for long-term safety. Statistically significant ↑ risk for pancreatitis or neoplasms was not shown in this trial or the other incretin trials. However, the authors acknowledge the follow-up may not have been long enough to rule out this possibility.5
- Effect of lixisenatide on microvascular outcomes (e.g., retinopathy, neuropathy, nephropathy) as these may take 5-10+ years to develop and median trial follow-up was 2.1 years.
- Currently it is available in the UK for about £54.14 for 28 days and unavailable in Canada or the US.6
- A study examining the cost/QALY gained of exenatide vs. lixisenatide in T2DM patients (looking at T2DM complications, weight, adverse effects and costs) with a 40-year time horizon showed that lixisenatide is not as cost-effective compared to exenatide. Cost/ QALY gained with exenatide versus lixisenatide was £10,002 compared with much lower costs for dulaglutide and lixisenatide.3


HOW DOES ELIXA COMPARRE TO OTHER DIABETES TRIALS?1
- Neutral CV outcome for lixisenatide similar to EXAMINE7 (alogliptin add-on vs. usual care) and TECOS10 (sitagliptin as an add-on vs. usual standard of care).
  - In alogliptin EXAMINE7, 88% of the patients had a history of MI while lixisenatide ELIXA had only 22%.9,11
  - In alogliptin EXAMINE7 patients were more unstable compared to lixisenatide ELIXA (45 days vs. 72 days from index ACS case to randomization).3
- Lack of beneficial outcomes for lixisenatide compared to EMPA-REG12 (empagliflozin add-on vs. usual care), LEADER13 (lixisenatide as an add-on vs. usual standard of care), and SUSTAIN-614 (semaglutide add-on vs. usual care; results not yet published in peer-reviewed trial).
  - Since T2DM patients have a 2-3x increased risk for developing CV disease and >60% of deaths are due to CV complications,5 agents with promising CV protection like empagliflozin EMPA-REG, lixisenatide LEADER and semaglutide SUSTAIN-6 (not available in CA) may be preferred.

Remember...
- For vascular protection, CDA 2013 (updated 2016) recommends: lifestyle (nutrition, exercise, smoking cessation); optimal HbA1c control (usually ≤7%); BP control (<130/80 mmHg), and cholesterol control (LDL ≤2 mmol/L); and lastly CV protective drugs (i.e., ACEI/ARB, statin, ASA [if indicated])15

RELATED RxFiles LINKS
- RxFiles Diabetes Agents Outcomes Table: http://www.rxfiles.ca/rxfiles/uploads/documents/Diabetes-Agents-Outcome-Comparison-Summary-Table.pdf

Note: This document is a summary of the RxFiles Trial Summary dated July 2016. For the most current and comprehensive information, please visit the RxFiles website at www.rxfiles.ca.
References:


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