ELIXA: Lixisenatide [LYXUMIA, ADLYXIN] CV Outcomes Trial Summary[1]

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 [1]

***Lixisenatide* versus *placebo plus standard care*: not too bad but nothing really good either. (Note – currently not available in Canada)** [July 2016]

- 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 (GLP1-A) 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.[2,3] Approved by the FDA July 2016.
- Non-inferior outcome trial mandated by the FDA to ensure CV safety in the "post-rosiglitazone era".[4]

TRIAL BACKGROUND[1,5-7]

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). Enrollment/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.

INCLUSION: T2DM patients with **recent (≤180 days) ACS event** (median time to randomization: 72 days post-ACS event).

EXCLUSION: Age <30 yrs, PCI within previous 15 days, CABG following qualifying ACS event, planned coronary revascularization ≤90d after screening, eGFR<30ml/min/1.73m^2, 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 ± 9.7yrs, ~69% ♂, **eGFR** 76± 21(mL/min/1.73m^2), LDL 2.03± 0.9 mmol/L, SBP 130 ± 17mmHg; **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/m^2; **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[1]

Follow-up: median 2.1 year

TABLE 1: EFFICACY & SAFETY NON-INFERIORITY DATA {NNT/H = number needed to Treat for Benefit / Harm}

CLINICAL ENDPOINTS ITT ANALYSIS	LIXISENATIDE (20MCG) n=3034	PLACEBO n=3034	HR (95% CI)	P VALUE	ARR/ARI	NNT/NNH /25 MON.	COMMENTS
PRIMARY ENDPOINT							
CV death, non-fatal MI, non-fatal stroke or unstable angina (first event)	13.4% (n=406)	13.2% (n=399)	1.02 (0.89-1.17)	P<0.001 (non-inferiority) 0.81 (superiority)			• **HbA1c** ↓ by 0.27% (-0.31 to -0.22%). • **Systolic BP** ↓ by 0.8mmHg (-1.3 to -0.3mmHg). • **Weight** ↓ by 0.7 kg (-0.9-to -0.5kg). • 85.5% in lixisenatide group took max dose, 96.5% in placebo took volume matched max dose at end of the study.
- CV death (all events)	5.1% (n=156)	5.2% (n=158)	0.98 (0.78-1.22)	0.85			
- MI (all events)	8.9% (n=270)	8.6% (n=261)	1.03 (0.87-1.22)	0.71			
SECONDARY ENDPOINTS							
1° endpoint or hospitalization for HF	15% (n=456)	15.5% (n=469)	0.97 (0.85-1.10)	0.63			
1° endpoint, hospitalization for HF or revascularization	21.8% (n=661)	21.7% (n=659)	1.00 (0.90-1.11)	0.96	--	--	
Hospitalization for HF	**4% (n=122)**	**4.2% (n=127)**	**0.96 (0.75-1.23)**	**0.75**	--	--	
-with no prior HF	2.4% (56/2352)	2.5% (58/2358)	0.97 (0.67-1.40)	0.87 for interaction	--	--	
-with prior HF	9.7% (66/682)	10.2% (69/676)	0.93 (0.66-1.30)		--	--	
Death from any cause	7% (n=211)	7.4% (n=223)	0.94 (0.78-1.13)	0.5	--	--	

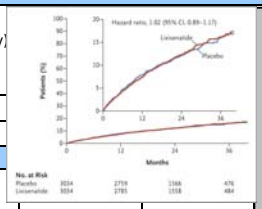

TABLE 2: ADVERSE EVENTS {NNT/H = number needed to Treat for Benefit / Harm}

CLINICAL ENDPOINTS	LIXISENATIDE n=3034	PLACEBO n=3034	P VALUE	ARR/ARI (POOLED)	NNT/NNH /25 MON.	COMMENTS
Adverse events leading to discontinuation	11.4% (n=347)	7.2% (n=217)	<0.001	4.2%	24	-**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.
GI event leading to discontinuation	4.9% (n=149)	1.2% (n=37)	<0.001	3.7%	28	
Nausea	3% (n=91)	0.4% (n=11)	<0.001	2.6%	39	
Vomiting	1.1% (n=33)	0.2% (n=5)	<0.001	0.9%	112	
Serious adverse events (SAE)	20.6% (n=625)	22.1% (n=669)	--	--	--	
Hypoglycaemic events	16.6% (n=504)	15.2% (n=462)	p=0.14	--	--	
Urine albumin/creatinine ratio	+26%	+32%	0.07	--	--	

STRENGTHS, LIMITATIONS, & UNCERTAINTIES[1]

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 greater 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 liraglutide was £10,002 compared with much lower costs for dulaglutide and liraglutide.[8]
- **Trials recently completed for GLP1-A:** **SUSTAIN6**(semaglutide); results not published in peer-reviewed trial and **ongoing:** **EXSCEL**(exenatide)(2018), **REWIND**(dulaglutide)(2018), **HARMONY**(albiglutide)(2019).

HOW DOES ELIXA COMPARE TO OTHER DIABETES TRIALS? [1]

- Neutral CV outcomes for lixisenatide similar to **EXAMINE**[9] (alogliptin add-on vs. usual care) and **TECOS**[10] (sitagliptin as an add-on vs. usual standard of care).
  - In alogliptin[EXAMINE], 88% of the patients had a history of MI while lixisenatide[ELIXA] had only 22%.[9,11]
  - In alogliptin[EXAMINE], patients were more unstable compared to lixisenatide[ELIXA] (45days vs. 72 days from index ACS case to randomization).[8]
- Lack of beneficial outcomes for lixisenatide compared to **EMPA-REG**[12] (empagliflozin add-on vs. usual care), **LEADER**[13] (liraglutide as an add-on vs. usual standard of care), and **SUSTAIN-6**[14] (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] liraglutide, [LEADER] and semaglutide [SUSTAIN-6] (not available in CAN) 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-Outcomes-Comparison-Summary-Table.pdf
- RxFiles Diabetes – Landmark Trials and Links: http://www.rxfiles.ca/rxfiles/uploads/documents/CHT-Diabetes-Landmark-Trials-Links.pdf
- RxFiles Diabetes—**EMPA-REG:** CV Outcomes Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/EMPA-REG%20Trial%20Summary.pdf
- RxFiles Diabetes—**LEADER:** CV Outcomes Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/Leader-Liraglutide%20VICTOZA%20and%20Cardiovascular%20Outcomes%20in%20Type%202%20Diabetes.pdf
- RxFiles Diabetes—**TECOS** CV Outcomes Trial Summary http://www.rxfiles.ca/rxfiles/uploads/documents/TECOS-Trial-Summary.pdf

✗ =non-formulary in SK ⊗=not covered by NIHB ☎=Exceptional Drug Status in SK ♀=female ♂=male **AE**=adverse event **ACS**=acute coronary syndrome **BMI**=body mass index **CABG**=coronary artery bypass graft **CAD**=coronary artery disease **CV**= cardiovascular **CVD**=cardiovascular disease **DPP4-I**=dipeptidyl peptidase-4 inhibitor **eGFR**= estimated glomerular filtration rate **FDA**= Food and Drug Administration **GI**=gastrointestinal **GLP1-A**=glucagon-like peptide-1 agonist **HbA1c**= hemoglobin A1c **HF**=heart failure **HTN**=hypertension **LDL**=low density lipoprotein **NSTEMI**= non-ST-segment elevation myocardial infarction **MI**=myocardial infarction **NR**=not reported **PAD**=peripheral artery disease **PCI**= percutaneous intervention **SBP**=systolic blood pressure **SGLT2-I**=sodium glucose cotransporter 2 inhibitor **SU**=sulfonylurea **STEMI**= ST-segment elevation myocardial infarction **subcut**= subcutaneous **T2DM**=type 2 diabetes mellitus **TZD**=thiazolidinedione

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