Sotagliflozin to Improve Glycemic Control in Adults with Type 1 Diabetes (T1D) Mellitus and Chronic Kidney Disease (CKD)

October 31, 2024

Endocrinologic and Metabolic Drugs Advisory Committee

Lexicon Pharmaceuticals, Inc.

Introduction: T1D-CKD Indication

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Insulin Therapy is a Necessary and Life-Saving Intervention for People with Type 1 Diabetes

- Despite advances in insulin treatments only ~20% of people achieve optimal glycemic control[1]
- Poor glycemic control* increases morbidity and mortality risk[2-5]
- Mortality and morbidity risks in patients with T1D vs the overall population:
  - **10X** greater risk cardiovascular disease[2]
  - **6X** greater risk of ESKD[5]
  - **4X** greater risk of HF hospitalization[3]
  - **2-5X** greater risk of all-cause mortality[4]

* Hypo- or hyperglycemia episodes outside the recommended blood glucose target range

1. Pettus, 2019; 2. de Ferranti, 2014; 3. Rosengren, 2015; 4. Ruiz, 2022; 5. Rosolowsky, 2011

Sotagliflozin an Oral Dual Inhibitor of SGLT1 and SGLT2 Improves Glycemic Control

- Adjunct therapy for use with insulin
- SGLT1 inhibition in intestinal tract blunts and delays glucose absorption and reduces postprandial glucose excursions[1]
- SGLT2 inhibition in kidney reduces glucose reabsorption and increases urinary glucose excretion, lowering blood glucose[2]

1. Dobbins, 2015; 2. Rieg, 2014

Sotagliflozin Development Program Includes Three Phase 3 Studies in Patients with T1D

T1D

Study 309

Phase 3, randomized, double-blind, placebo-controlled

Sotagliflozin 200 mg and 400 mg

T1D (N = 793)

Study 310

Phase 3, randomized, double-blind, placebo-controlled

Sotagliflozin 200 mg and 400 mg

T1D (N = 782)

Study 312

Phase 3, randomized, double-blind, placebo-controlled

Sotagliflozin 400 mg

T1D (N = 1,405)

- **Statistically significant benefits**
- **Improved glycemic control**
- **Consistent benefit across subgroups**

Statistically significant primary and key secondary endpoints ($p < 0.001$)

Sotagliflozin Re-Submission for T1D-CKD Subgroup Following CRL* for 2018 NDA in Adults with T1D

Evidence of Efficacy in Patients with T1D

- ✓ Statistically significant A1C reduction
- ✓ Effects across clinically relevant secondary endpoints

Safety Benefits and Concerns

- ✓ No increase in severe hypoglycemic events
- ✗ Increased occurrence of diabetic ketoacidosis (DKA)

Jan 2019	**EMDAC Meeting**	Voted 8-8 on benefit-risk of sotagliflozin in overall T1D Population
Mar 2019	**CRL Issued**	Need for additional benefits that outweigh DKA risk
Dec 2023	**Type A Meeting**	Identification of a subpopulation from Phase 3 program with improved benefits and/or diminished risk
Mar 2024	**Type A Meeting**	T1D-CKD a reasonable subgroup for NDA resubmission

CRL: Complete Response Letter

Since CRL, Sotagliflozin Demonstrated Cardiorenal Benefits in SCORED Study

T2D

SCORED Study

Phase 3,
randomized, double-blind,
placebo-controlled

Patients with T2D, CKD,
and other CV risk factors
N = 10,584

Sotagliflozin
200 to 400 mg

INPEFA® Sotagliflozin Approval in 2023

To reduce risk of CV death, hospitalization for heart failure, and urgent heart failure visit in adults with heart failure, or T2D, chronic kidney disease, and other CV risk factors

Potential to benefit patients with T1D and CKD

Patients with T1D-CKD have Greater Unmet Need for Improved Glycemic Control and Controlling CKD Risks

CKD is independent predictor for increased morbidity and mortality

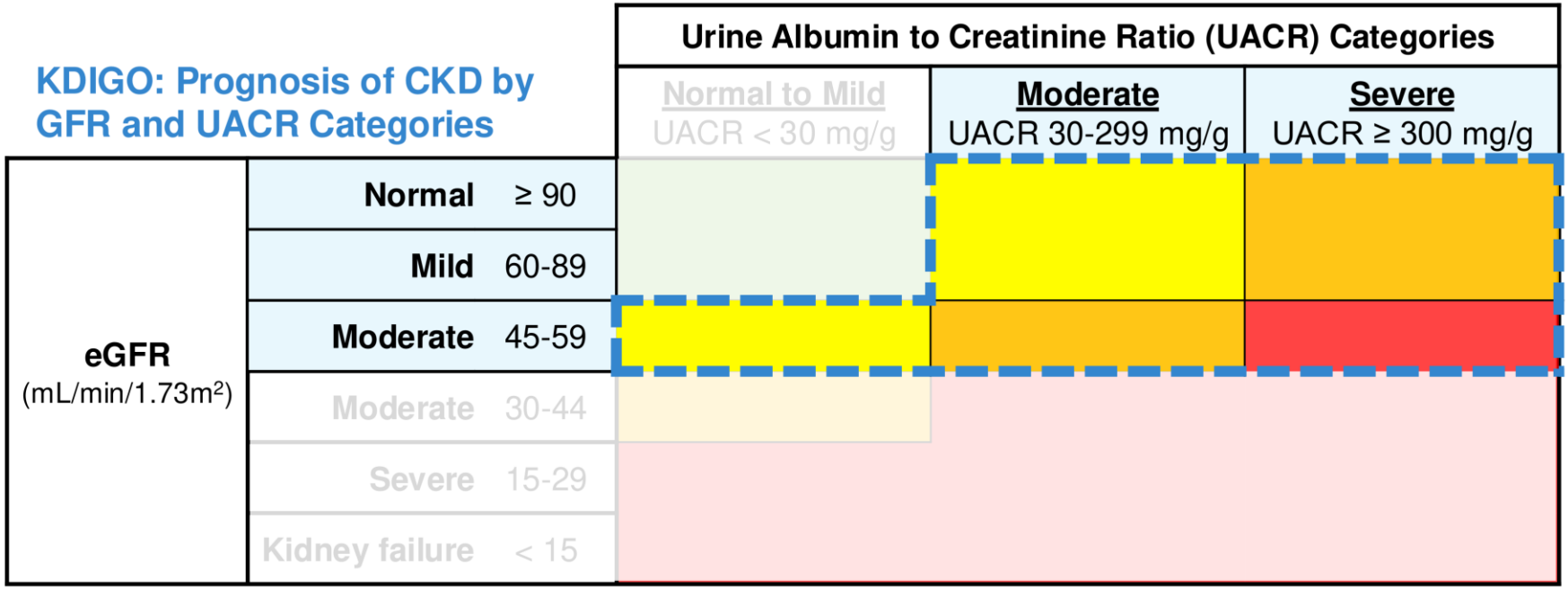
- Poor glycemic control associated with accelerated eGFR decline[1] and more rapid progression to ESKD[2]
- eGFR decline associated with increased risk of hospitalization for HF[3]
- Decreased time in range associated with elevation in risk for kidney complications[4]
- Increased risk of death[5]

Patients with T1D-CKD represent high-risk subset who would gain additional benefits from improved glycemic control

1. Shah, 2024; 2. Skupien, 2014; 3. Rosengren, 2015 ; 4. Beck, 2019 ; 5. Liao, 2023

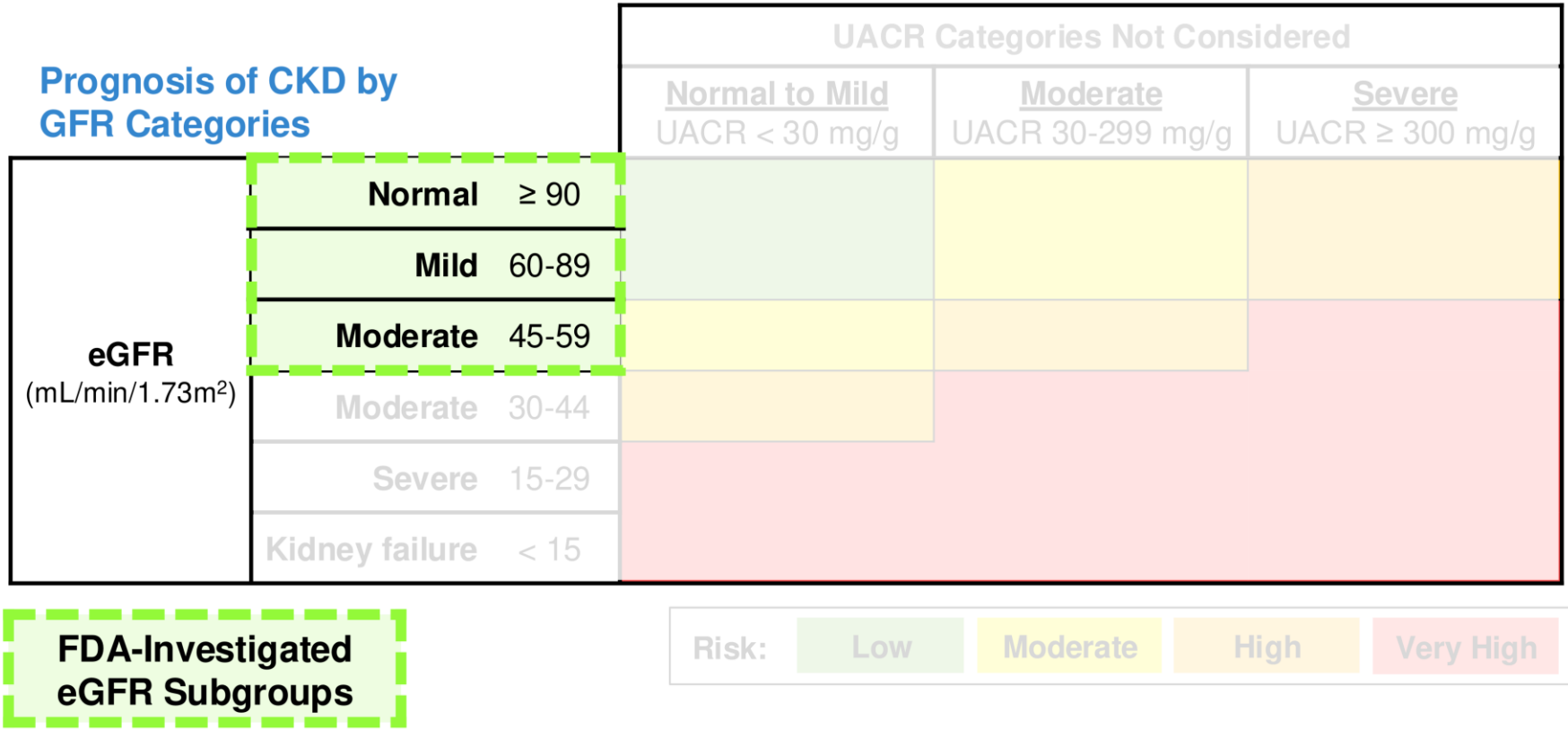
Lexicon Defined T1D-CKD Subgroup with Greatest Need to Slow Disease Progression

KDIGO: Prognosis of CKD by GFR and UACR Categories

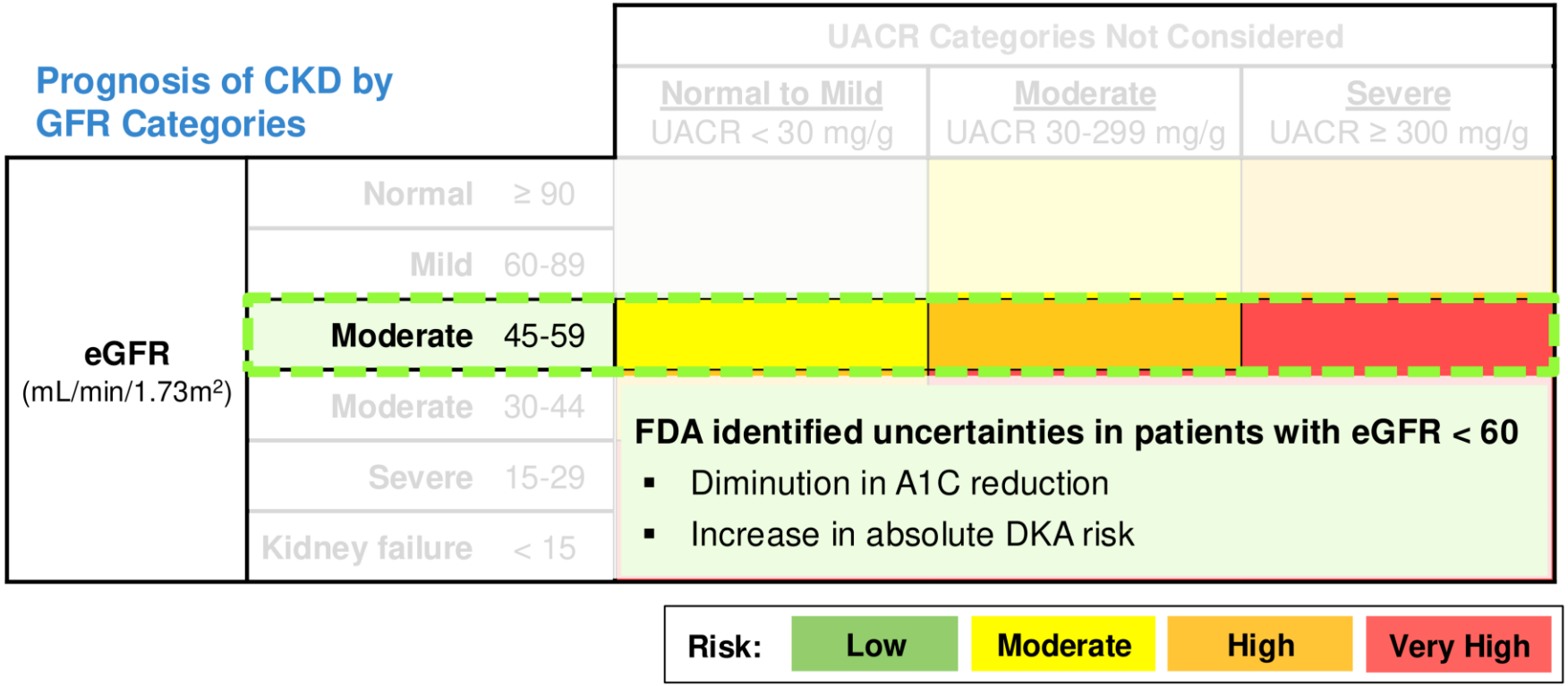


Kidney Disease: Improving Global Outcomes (KDIGO) Diabetes Work Group. Kidney Int, 2022

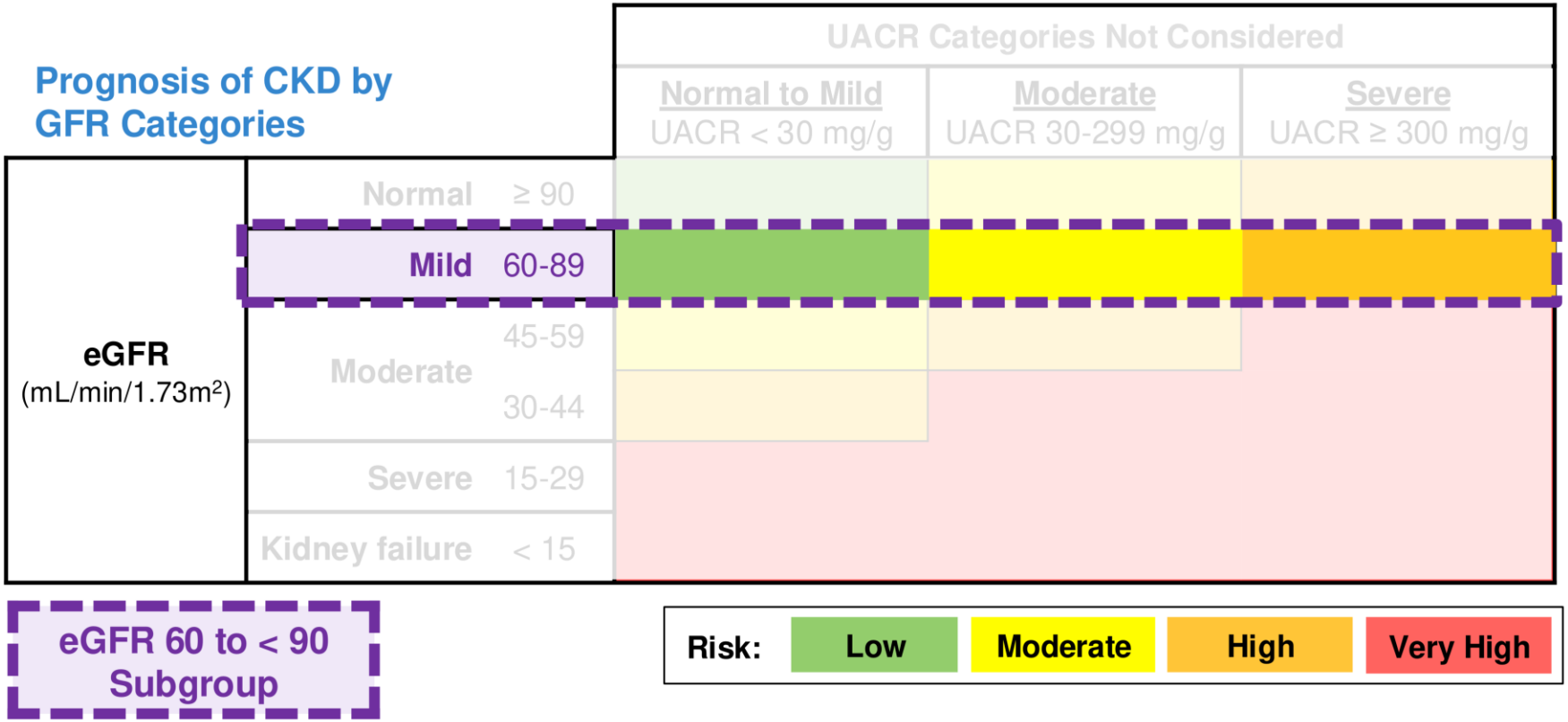
FDA Analyses Evaluate Subgroups Based on eGFR



Evidence Highlights Uncertainties Around Efficacy and Safety in Subgroup of Patients with eGFR <60



eGFR 60 to < 90 Subgroup Has High Unmet Need and Removes Uncertainties in Patients with eGFR < 60



T1D-CKD Subgroup Improves Benefit-Risk Compared to Overall T1D Population

Overall Population

- Statistically significant A1C Reductions
- Reduction in Level 2 hypoglycemia events
- No Increased risk of Level 3 (severe) hypoglycemia
- Increased risk of DKA

2019 EMDAC Voted 8-8 Benefit-Risk

T1D-CKD

- Consistent efficacy and safety profile compared to overall population
- Most advanced CKD; population with greatest unmet need
  - Incremental benefits from similar efficacy
- SCORED supports potential long-term benefit on clinical outcomes

Improved Benefit-Risk vs Overall Population

eGFR 60 to < 90

- Removes uncertainties in patients with eGFR < 60
- Retains mild to moderate risk population that needs to slow disease progression

Improved Benefit-Risk vs Overall Population

T1D Development Program Provides Data Supporting T1D-CKD and eGFR 60 to < 90 Subgroups

T1D

Study 309

Phase 3, randomized, double-blind, placebo-controlled

Sotagliflozin 200 mg and 400 mg

T1D (N = 793)

T1D-CKD (N = 116)

eGFR 60 to < 90 (N = 430)

Study 310

Phase 3, randomized, double-blind, placebo-controlled

Sotagliflozin 200 mg and 400 mg

T1D (N = 782)

T1D-CKD (N = 118)

eGFR 60 to < 90 (N = 344)

Study 312

Phase 3, randomized, double-blind, placebo-controlled

Sotagliflozin 400 mg

T1D (N = 1,405)

T1D-CKD (N = 224)

eGFR 60 to < 90 (N = 612)

Sotagliflozin Proposed Indication and Dosing in T1D-CKD Population

Adjunct to insulin therapy to improve glycemic control in adults with T1D and CKD

Recommended Oral Daily Dose

- 200 mg QD, ≤ 1 hour before first meal of the day
- May be increased to 400 mg QD for patients requiring additional glycemic control

Agenda

Overview of T1D-CKD Disease, Burden and Unmet Need	**Steven Edelman, MD** Professor of Medicine University of California, San Diego
Results in T1D-CKD Subgroup	**Michael Davies, PhD** Executive Director, Clinical Development Lexicon Pharmaceuticals
Results in eGFR 60 to < 90 Subgroup	**Craig Granowitz, MD, PhD** Senior Vice President and Chief Medical Officer Lexicon Pharmaceuticals
Results in Patients with Diabetes and More Advanced Kidney Disease	**Craig Granowitz, MD, PhD**
T1D-CKD Management, Risk Management, and Education	**Richard Pratley, MD** Medical Director at the AdventHealth Diabetes Institute Senior Investigator, Diabetes Program Lead at the Translational Research Institute
Conclusion and Q&A	**Craig Granowitz, MD, PhD**

Additional Experts

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Executive Director, Drug Safety
Lexicon

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Executive Director, Head of Regulatory Affairs
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Overview of T1D-CKD Disease, Burden and Unmet Need

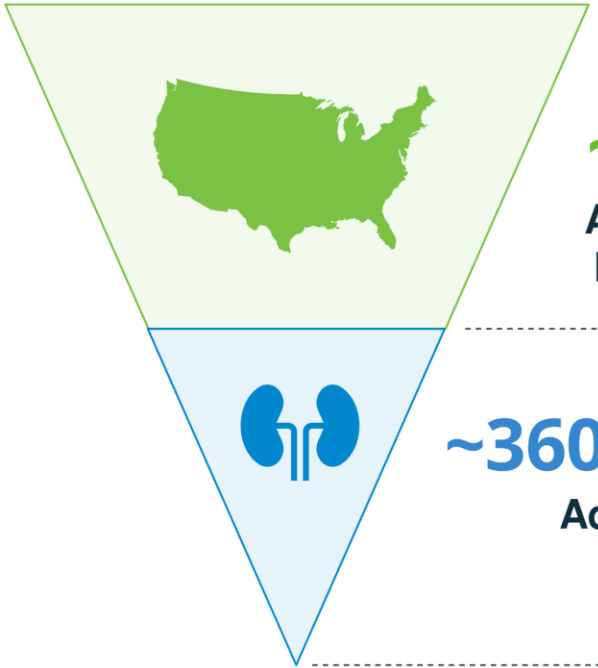
Steven Edelman, MD

Professor of Medicine
Division of Endocrinology, Diabetes & Metabolism
University of California, San Diego

Founder and Director
Taking Control of Your Diabetes
https://tcoyd.org/

People with Type 1 Diabetes Face Significantly Higher Risks of Morbidity and Mortality

CO-19



~1.7M
Adults report having T1D[1]

~360,000 (21%)
Adults with T1D have CKD[2]

T1D vs Overall Population

10X	Greater Risk Cardiovascular Disease[3]
6X	Greater Risk End-Stage Kidney Disease[6]
4X	Greater Risk Heart Failure Hospitalization[4]
2-5X	Greater Risk All-Cause Mortality[5]

CKD is Independent Predictor of Increased Morbidity and Mortality

1. CDC National Diabetes Statistics Report, 2024; 2. Rossing, 2024; 3. de Ferranti, 2014; 4. Rosengren, 2015; 5. Ruiz, 2022; 6. Rosolowsky, 2011

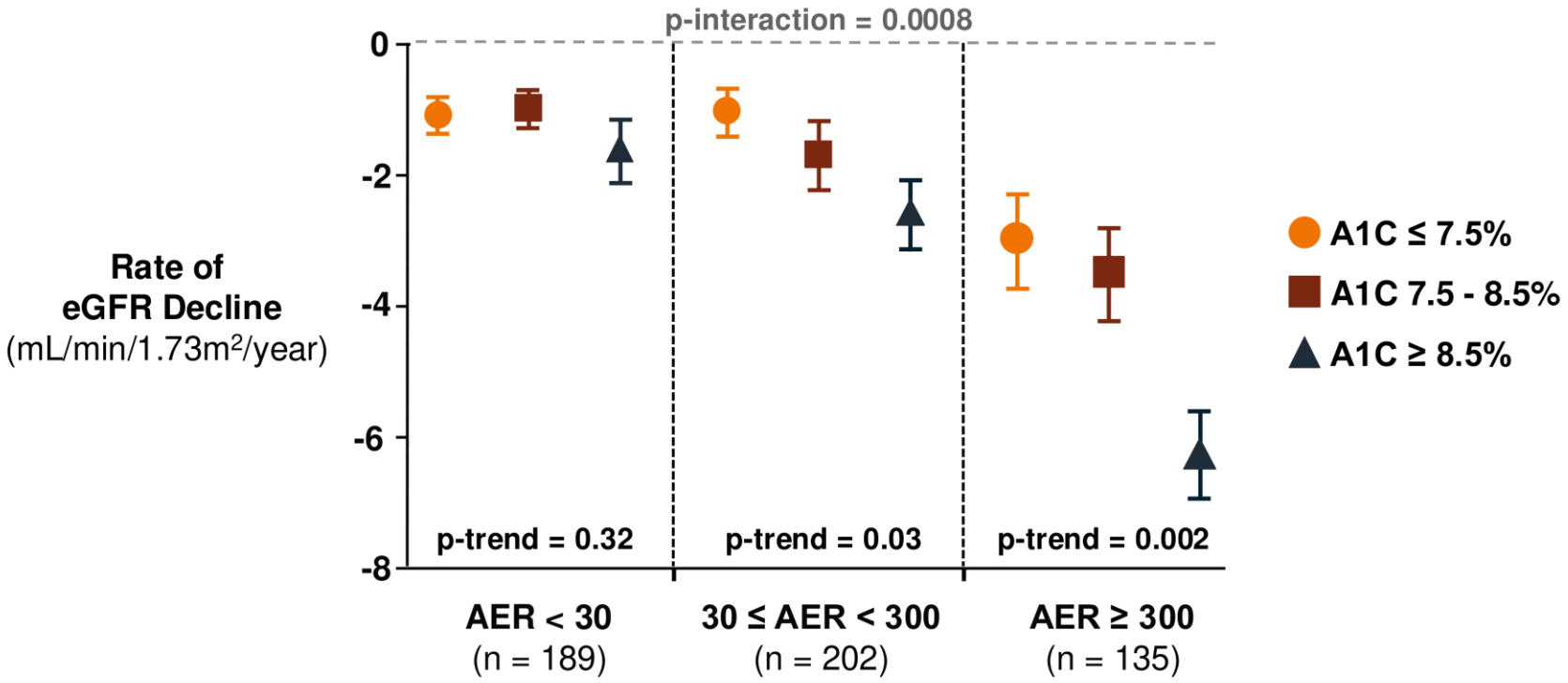
Most Patients with Type 1 Diabetes Do Not Meet Glycemic Control Targets with Insulin Alone

Glycemic Control in T1D		
	~20% A1C < 7%[1]	~50% A1C > 8%[2]

- Patients not achieving A1C targets remain at significantly greater risk of complications associated with their condition

1. Akturk, 2023; 2. Guanghong and Renard, 2020

Glycemic Control Impacts Kidney Function Decline Among People with Type 1 Diabetes and CKD

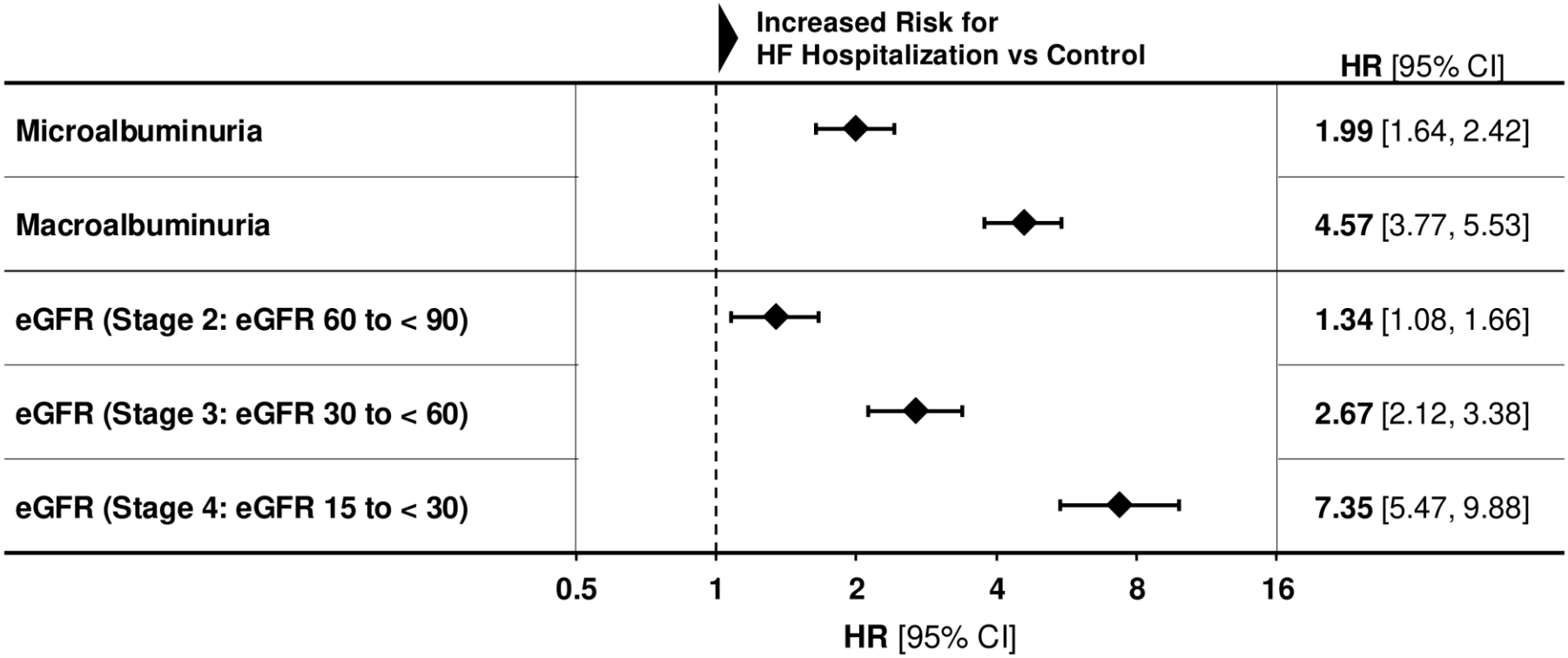


Shah, 2024

AER: Albumin excretion rate

Data points represent beta estimates (±SE) from mixed-effects linear regression models

eGFR Decline and Albuminuria Associated with Hospitalization for Heart Failure in Patients with T1D



Rosengren, 2015
Adjusted for age, sex, diabetes duration, education, birth in Sweden, comorbidities, mean HDL-C and LDL-C, and treatment with lipid-lowering drugs.

Diabetes Management Aims to Minimize Disease Progression Through Improved Glycemic Control

Goals of Treatment in T1D-CKD

- ✓ Reduce risk of CV, ESKD, retinopathy, neuropathy, other complications
- ✓ Achieve glycemic targets A1C < 7.0%
  - ✓ Improve time in range
- ✓ Lower body weight and blood pressure
- ✓ Improve lipid control

Challenges with Current Glycemia Treatments Have Impacted Patients Ability to Reach A1C Goals

- Limited therapeutic options for patients with T1D-CKD
- No approved oral agents to improve glycemia
- EMDAC acknowledged
  - Existing therapies are inadequate
  - More effective, convenient glucose management options needed
- Patients experience excessive weight gain and peripheral insulin resistance, reduced quality of life

Hypoglycemia and Diabetic Ketoacidosis (DKA)

Clinicians and Patients Seek Glycemic Control Without Hypoglycemia or DKA

- Hypoglycemia and DKA are acute, serious, potentially life-threatening metabolic complications of T1D[1]

Severe Hypoglycemia

5% of T1D hospitalizations[2]

4-10% of deaths[3]

DKA

0.7% of T1D hospitalizations[2]
in patients with A1C < 8%

0.4% of deaths[4]

1. Peters, 2020; 2. Pettus, 2020; 3. Seaquist, 2013; 4. Ehrmann, 2020

Standard of Care for Diagnosing and Managing DKA Based on Consensus Statements and Guidelines[1,2]

Diagnostic Criteria	
Diabetes	Check blood glucose or history of Diabetes
Ketosis	Check urine or serum ketones at any early warning sign or illness
Acidosis	Check for metabolic acidosis and its associated symptoms (nausea, fatigue abdominal pain, shortness of breath)

Management [STICH Protocol]	
ST	**Stop** SGLT2i (if using) until ketones are back to baseline
I	**Inject** short acting insulin
C	**Consume** 30-60 g carbohydrate
H	**Hydrate** with 8-16 oz of fluid

Recheck ketones every 3-4 hours and if **symptoms persists** or ketosis does not resolve within 4-6hrs, **seek emergency care**

1. Umpierrez, 2024; 2. Garg, 2018

Summary of Unmet Need for Patients with T1D-CKD

- Patients with T1D and CKD are at an increased risk of glycemic and kidney complications[2]
- Most patients do not achieve A1C targets with insulin alone
- Outcomes influenced by patient engagement and glucose monitoring
  - CGM, insulin pump, ketone monitoring when suspect episode
- SGLT inhibitors proven benefit in reducing HF, CKD, and death in T2D
  - Pathophysiology of CKD in T2D and T1D is similar[1]
- Urgent need for a new adjunct therapy
  - Improve glycemic control
  - Diminish long-term complications from uncontrolled diabetes

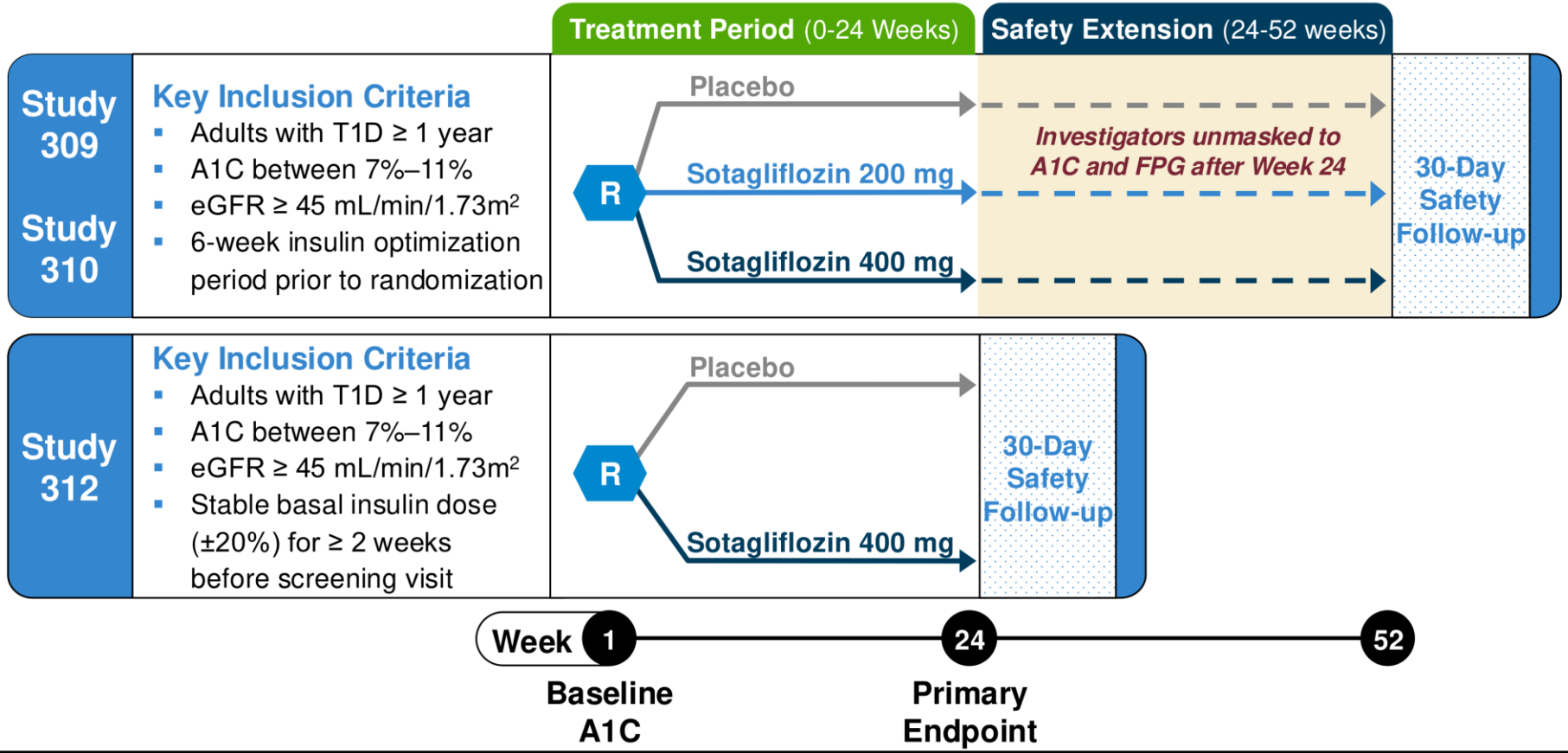
1. DiVincenzo, 2020; 2. American Diabetes Association Professional Practice Committee, 2024

Efficacy and Safety in T1D-CKD Subgroup

Michael Davies, PhD

Executive Director, Clinical Development
Lexicon Pharmaceuticals, Inc.

Study Designs of Pivotal Phase 3 Studies



Overall Population: Phase 3 Primary Endpoints

	Study 309	Study 310	Study 312
Δ **A1C** (Week 24)	Primary < 0.001	Primary < 0.001	Secondary
A1C < 7.0% without SH or DKA (Week 24)	Secondary	Secondary	Primary < 0.001

T1D-CKD Subgroup Represents ~15% of Overall T1D Patients Enrolled in Phase 3 Studies

	Pooled Studies 309 / 310			Study 312	
	200 mg	400 mg	Placebo	400 mg	Placebo
Total Randomized	524	525	526	700	705
T1D-CKD subgroup, n (%)	**85** (16%)	**75** (14%)	**74** (14%)	**114** (16%)	**110** (16%)
eGFR ≥ 60 and UACR ≥ 30	**63** (74%)	**51** (68%)	**52** (70%)	**83** (73%)	**71** (64%)
eGFR of 45 to < 60	**22** (26%)	**24** (32%)	**22** (30%)	**31** (27%)	**39** (35%)

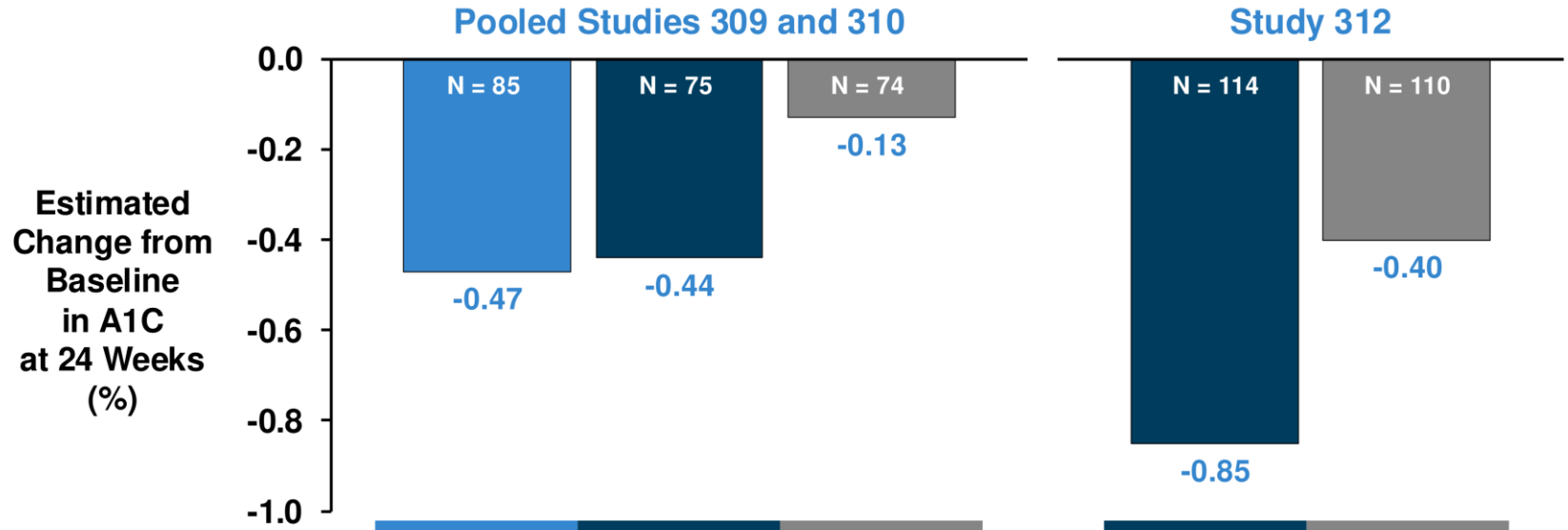
T1D-CKD: Baseline Demographics Similar Between Treatment Groups and Representative of US Population with T1D

		Pooled Studies 309 / 310			Study 312	
		200 mg N = 85	400 mg N = 75	Placebo N = 74	400 mg N = 114	Placebo N = 110
Age	**Mean** (years)	46.9	45.5	48.6	47.6	47.3
	≥ 65 years	15%	11%	19%	19%	15%
Sex	**Male**	59%	43%	46%	53%	50%
Race	**White**	93%	93%	93%	86%	82%
	Black	2%	1%	3%	6%	9%
Region	**US / Canada**	53%	43%	53%	41%	46%
BMI	**Mean** (kg/m^2)	29.2	28.7	29.3	28.7	28.3

T1D-CKD: Baseline Diabetes Characteristics Balanced Across Treatment Groups and Studies

	Pooled Studies 309 / 310			Study 312	
	200 mg N = 85	400 mg N = 75	Placebo N = 74	400 mg N = 114	Placebo N = 110
eGFR (mL/min/1.73m^2), mean	80.3	79.8	79.1	82.0	80.2
Normal (≥ 90)	29%	36%	31%	33%	35%
Mild (≥ 60 to < 90)	45%	32%	39%	32%	38%
Moderate (45 to < 60)	26%	32%	30%	36%	27%
UACR (mg/g), median	51	66	49	60	61
≥ 30 mg/g	87%	77%	82%	83%	80%
A1C (%), mean	7.7	7.9	7.8	8.3	8.7
≤ 8.5%	77%	75%	74%	46%	56%
Duration of T1D (years), mean	26.9	23.9	25.6	23.6	23.2
Insulin delivery via CSII	37%	39%	37%	41%	34%

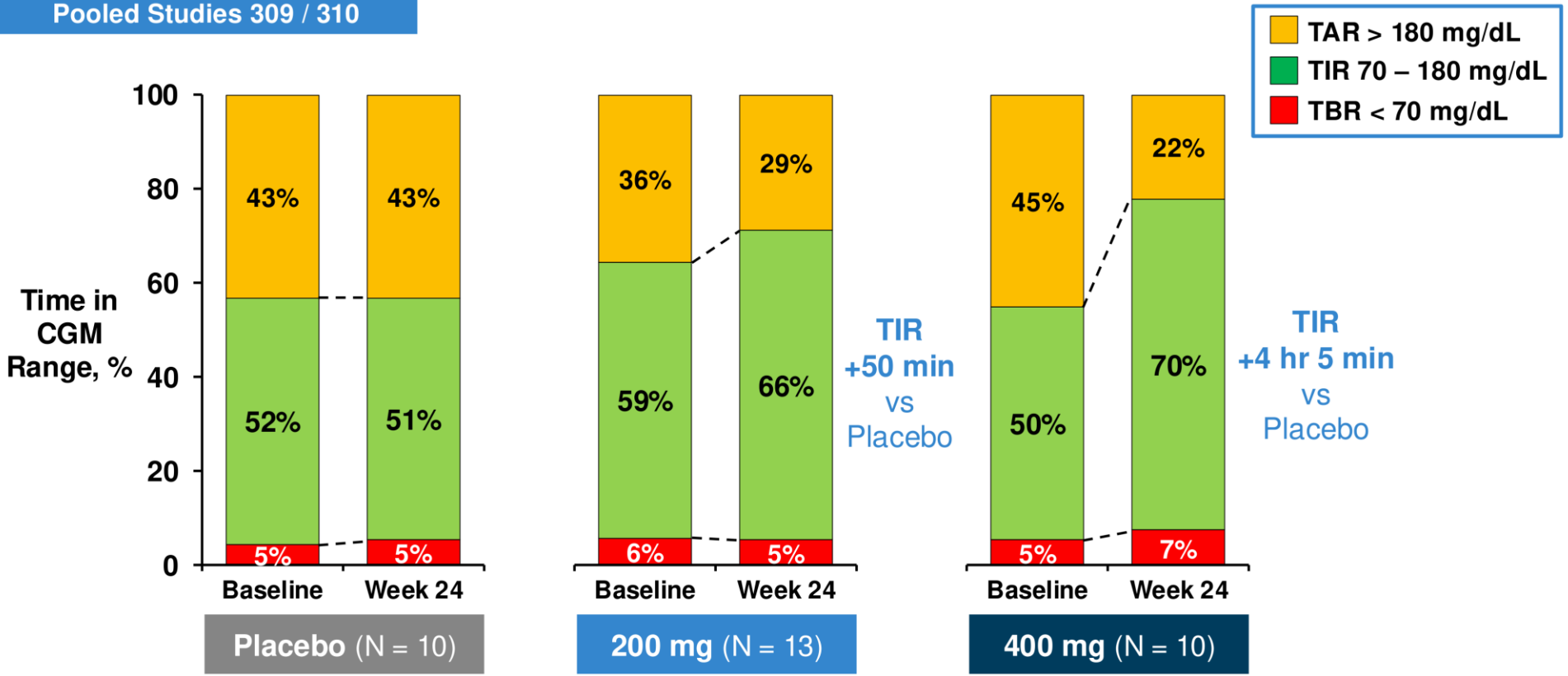
T1D-CKD: Sotagliflozin Demonstrated Significant A1C Reductions in Two Independent Datasets Through Week 24



	Pooled Studies 309 and 310			Study 312	
	200 mg	400 mg	Placebo	400 mg	Placebo
Baseline A1C (%)	7.7	7.9	7.8	8.7	8.3
Difference from Placebo [95% CI]	**-0.34** [-0.55, -0.12]	**-0.31** [-0.53, -0.09]		**-0.45** [-0.69, -0.21]	
Nominal p-value	**0.002**	**0.006**		**< 0.001**	

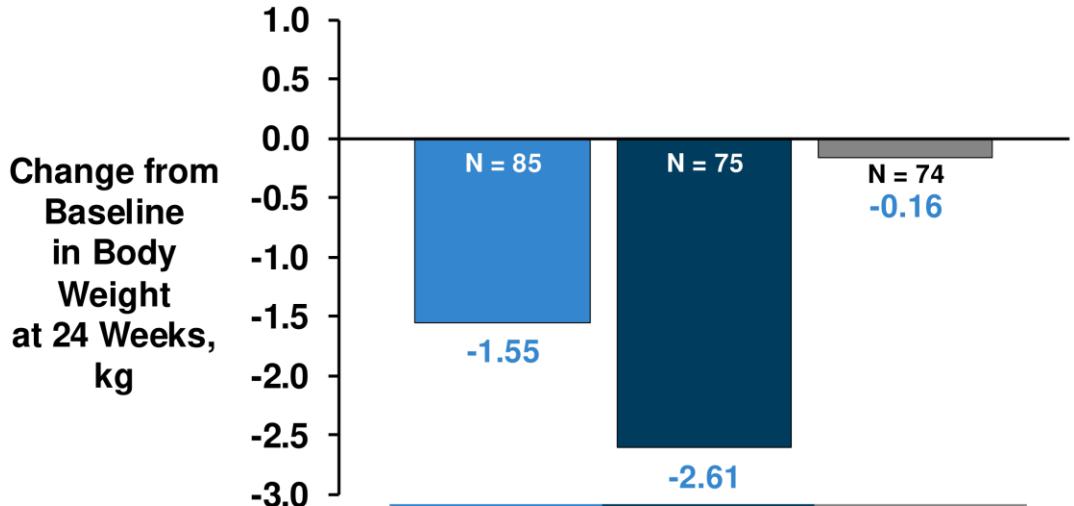
T1D-CKD: Sotagliflozin Increases Time in Range Using CGM Compared to Placebo

Pooled Studies 309 / 310



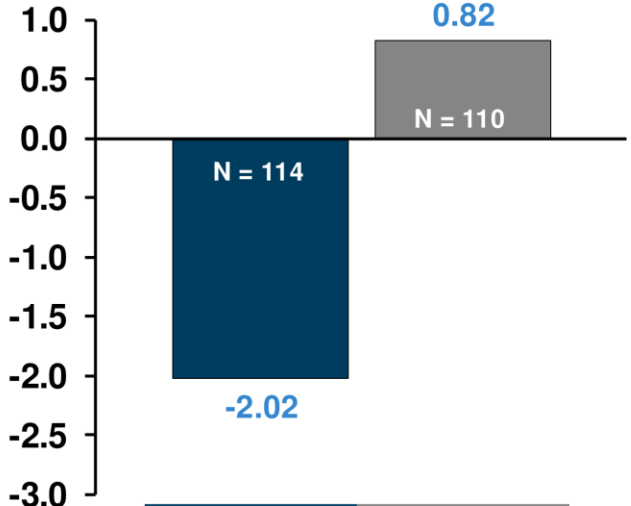
T1D-CKD: Significant Reductions in Body Weight Achieved with Sotagliflozin vs Placebo

Pooled Studies 309 / 310



	200 mg	400 mg	Placebo
Baseline body weight (kg)	86.7	83.4	85.0
Difference from Placebo [95% CI] kg	-1.39 [-2.33, -0.45]	-2.45 [-3.41, -1.49]	
Nominal p-value	0.004	< 0.001	

Study 312



	400 mg	Placebo
Baseline body weight (kg)	82.6	81.3
Difference from Placebo [95% CI] kg	-2.84 [-3.76, -1.91]	
Nominal p-value	< 0.001	

Safety in T1D-CKD Subgroup

T1D-CKD: 274 Participants Exposed to Sotagliflozin During Phase 3 T1D Development Program

	Pooled Studies 309 / 310 (52 weeks)			Study 312 (24 weeks)	
	200 mg	400 mg	Placebo	400 mg	Placebo
Number of patients	85	75	74	114	110
Exposure (days)**, mean**	339.1	332.4	319.8	150.0	154.9
Total patient-years of exposure	78.9	68.3	64.8	46.8	46.6

T1D-CKD: Safety Profile Similar to Placebo and Consistent with Overall Study Population

Proportion of Patients, %	T1D-CKD Subgroup					Overall T1D Population				
	Pooled Studies 309 / 310 (52 weeks)			Study 312 (24 weeks)		Pooled Studies 309 / 310 (52 weeks)			Study 312 (24 weeks)	
	200 mg N = 85	400 mg N = 75	Placebo N = 74	400 mg N = 114	Placebo N = 110	200 mg N = 524	400 mg N = 525	Placebo N = 526	400 mg N = 699	Placebo N = 703
Any AE	80%	68%	76%	59%	49%	75%	74%	71%	55%	53%
Any severe AE	13%	8%	14%	11%	6%	10%	9%	7%	6%	4%
Any serious AE	14%	11%	14%	11%	7%	10%	10%	7%	7%	3%
Any AE leading to discontinuation	4%	5%	5%	7%	4%	4%	7%	4%	6%	2%
Deaths	0	0	3%	0	0	0	0	0.6%	0.1%	0

Events occurring through end of treatment period

T1D-CKD: Similar Incidence of Common AEs Reported Between Treatment Groups Within Each Trial

AEs Reported in > 5% of Patients: Proportion of Patients, %	Pooled Studies 309 / 310 (52 weeks)			Study 312 (24 weeks)	
	200 mg N = 85	400 mg N = 75	Placebo N = 74	400 mg N = 114	Placebo N = 110
Any AE	80%	68%	76%	59%	49%
Urinary tract infection	13%	3%	7%	4%	5%
Diarrhea	9%	11%	4%	7%	3%
Blood ketone body increased	8%	5%	1%	5%	1%
Nausea	7%	5%	3%	7%	6%
Constipation	6%	1%	3%	2%	3%
Diabetic ketoacidosis	5%	7%	3%	3%	3%
Hypoglycemia	5%	1%	1%	5%	2%
Pollakuria	6%	0%	1%	4%	1%
Vulvovaginal mycotic infection	2%	7%	3%	1%	1%

Events occurring through end of treatment period

T1D-CKD: Sotagliflozin Did Not Result in Increase in AEs Leading to Study Drug Discontinuation

AEs Reported in > 1 Patient: Proportion of Patients, % (n)	Pooled Studies 309 / 310 (52 weeks)			Study 312 (24 weeks)	
	200 mg N = 85	400 mg N = 75	Placebo N = 74	400 mg N = 114	Placebo N = 110
Any AE leading to discontinuation	4% (3)	5% (4)	5% (4)	7% (8)	4% (4)
Diabetic ketoacidosis	0	1% (1)	0	2% (2)	0

Events occurring through end of treatment period

AEs of Interest

- Level 2 and Positively Adjudicated Severe Hypoglycemia
- Positively Adjudicated Diabetic Ketoacidosis

T1D-CKD: Sotagliflozin-Treated Patients Experienced Fewer Level 2 Hypoglycemia Events Relative to Placebo

Level 2 Hypoglycemia	T1D-CKD Subgroup					Overall T1D Safety Population				
	Pooled Studies 309 / 310 (52 weeks)			Study 312 (24 weeks)		Pooled Studies 309 / 310 (52 weeks)			Study 312 (24 weeks)	
	200 mg N = 85	400 mg N = 75	Placebo N = 74	400 mg N = 114	Placebo N = 110	200 mg N = 524	400 mg N = 525	Placebo N = 526	400 mg N = 699	Placebo N = 703
Patients, % (n)	91% (77)	89% (67)	89% (66)	72% (82)	84% (92)	92% (481)	92% (482)	91% (478)	76% (528)	80% (559)
Total events	1,002	1,120	1,390	670	713	7,129	7,133	8,995	3,512	4,682
Events per patient per year	12.7	16.4	21.5	14.3	15.3	14.9	15.0	19.0	11.8	15.4

Level 2 hypoglycemia = hypoglycemia events with blood glucose levels ≤ 55 mg/dL

T1D-CKD: Similar Rates of Positively Adjudicated Level 3 (Severe) Hypoglycemia Across Treatment Groups

Positively Adjudicated Level 3 (Severe) Hypoglycemia	T1D-CKD Subgroup					Overall T1D Safety Population				
	Pooled Studies 309 / 310 (52 weeks)			Study 312 (24 weeks)		Pooled Studies 309 / 310 (52 weeks)			Study 312 (24 weeks)	
	200 mg N = 85	400 mg N = 75	Placebo N = 74	400 mg N = 114	Placebo N = 110	200 mg N = 524	400 mg N = 525	Placebo N = 526	400 mg N = 699	Placebo N = 703
Patients, % (n)	**7%** (6)	**4%** (3)	**18%** (13)	**7%** (8)	**5%** (5)	**6%** (30)	**4%** (23)	**7%** (39)	**3%** (21)	**2%** (17)
Total events	**8**	**3**	**18**	**8**	**7**	**68**	**33**	**50**	**25**	**22**
EAIR / 100 PYE	**7.6**	**4.4**	**20.1**	**17.1**	**10.7**	**6.3**	**4.8**	**8.2**	**7.2**	**5.7**

EAIR: exposure adjusted incidence rate
Severe Hypoglycemia defined by ADA 2024 as a severe event characterized by altered mental and/or physical status requiring assistance for treatment of hypoglycemia, irrespective of glucose level

T1D-CKD: Increased Rate of Positively Adjudicated DKA in Sotagliflozin-Treated Patients

Positively Adjudicated DKA	T1D-CKD Population					Overall T1D Safety Population				
	Pooled Studies 309 / 310 (52 weeks)			Study 312 (24 weeks)		Pooled Studies 309 / 310 (52 weeks)			Study 312 (24 weeks)	
	200 mg N = 85	400 mg N = 75	Placebo N = 74	400 mg N = 114	Placebo N = 110	200 mg N = 524	400 mg N = 525	Placebo N = 526	400 mg N = 699	Placebo N = 703
Patients, % (n)	**5%** (4)	**3%** (2)	**1%** (1)	**3%** (3)	**1%** (1)	**3%** (15)	**4%** (20)	**0.2%** (1)	**3%** (21)	**0.6%** (4)
Total events	4	2	1	3	1	16	20	1	21	4
EAIR / 100 PYE	5.1	2.9	1.5	6.4	2.1	3.1	4.2	0.2	7.0	1.3

EAIR: exposure adjusted incidence rate
Potential DKA cases identified from AEs, laboratory values, signs, and/or symptoms suggestive of DKA

Efficacy and Safety Conclusion in T1D-CKD Subgroup

Efficacy

- Significant and consistent improvements in A1C in two independent study datasets that were similar to the overall population
- Improvements in body weight and time in range

Safety

- Similar safety profile to overall population
- Consistent reduction in Level 2 hypoglycemia rate
- No increased rate of Level 3 (severe) hypoglycemia
- Increased rate of DKA, similar to overall population

eGFR 60 to < 90 Subgroup

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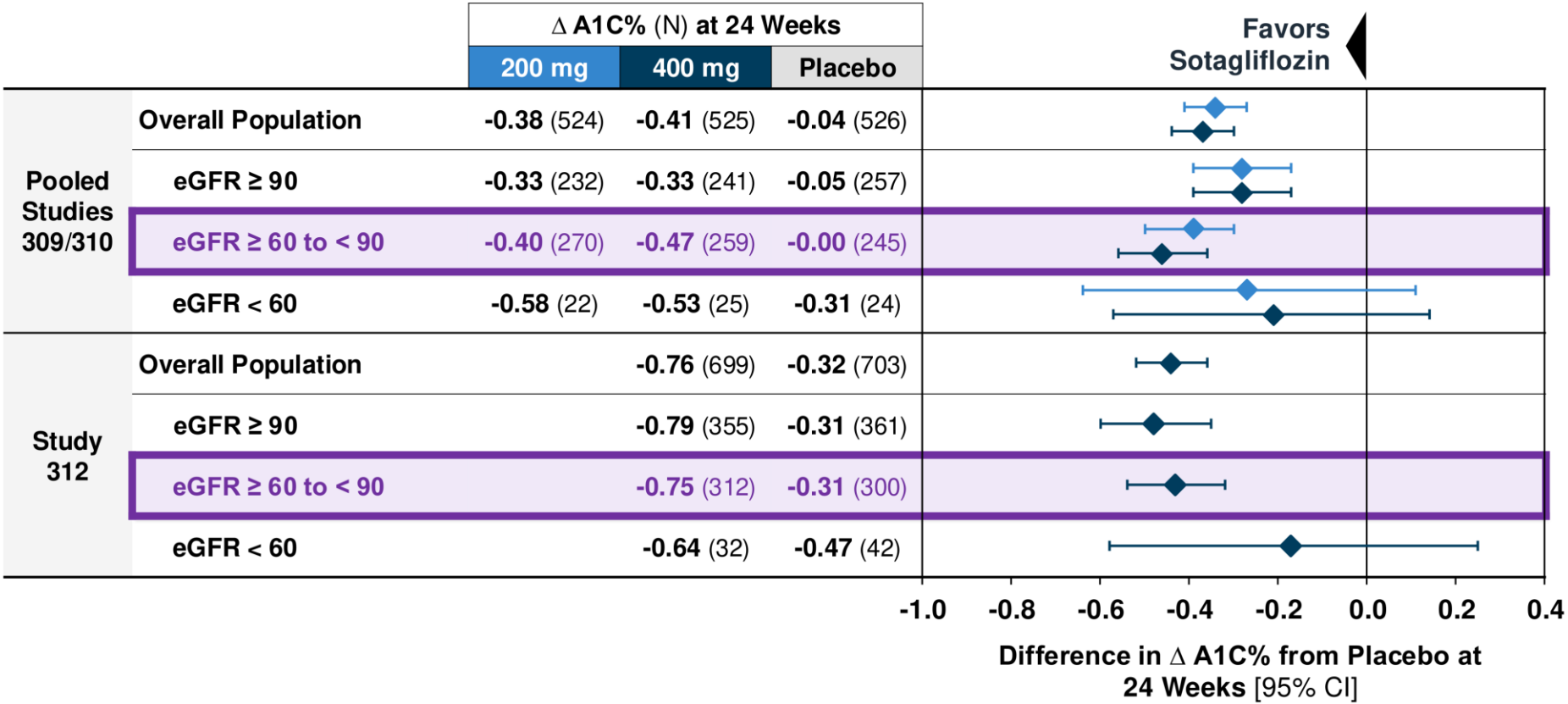
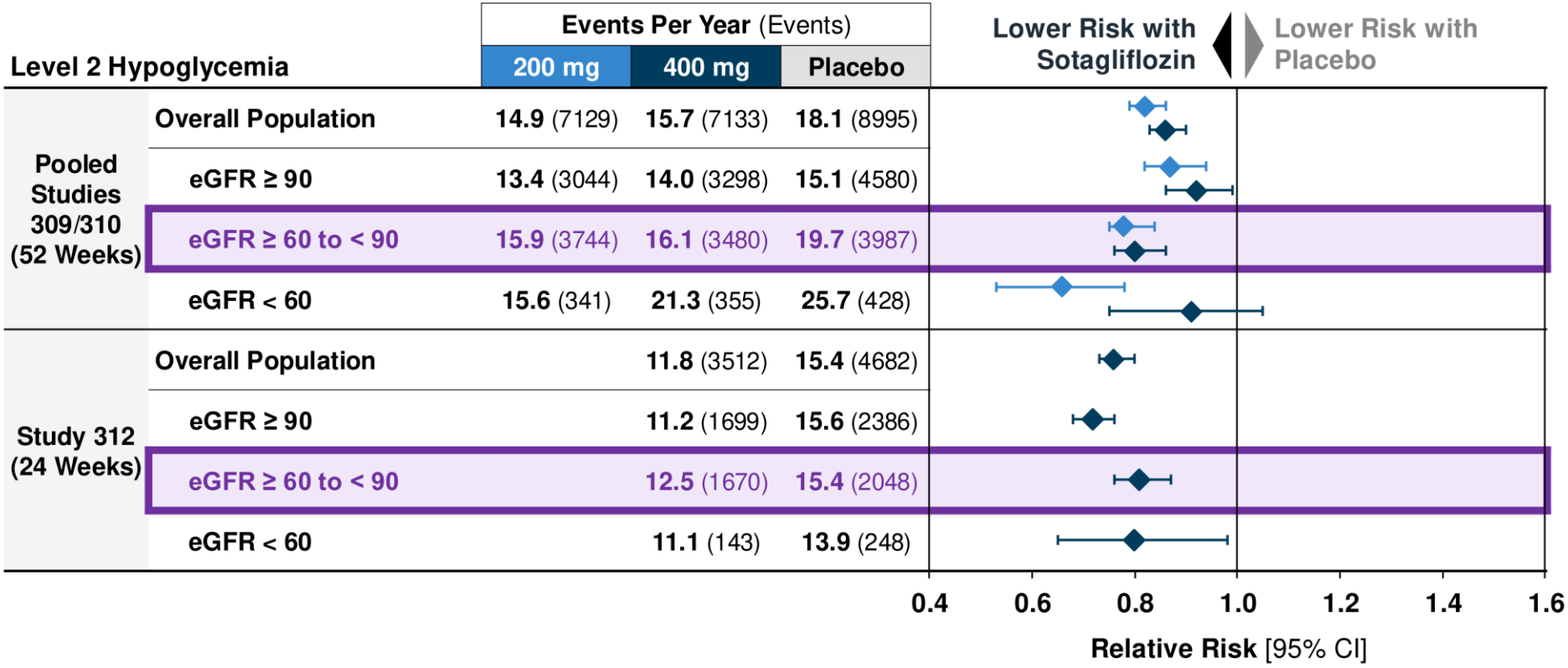
eGFR 60 to < 90 Subgroup: Represents ~47% of Overall Population

	Pooled Studies 309 / 310 (24 Weeks)			Study 312 (24 Weeks)	
	200 mg	400 mg	Placebo	400 mg	Placebo
Overall Population, N	**524**	**525**	**526**	**699**	**703**
eGFR ≥ 90, n (%)	232 **(44%)**	241 **(46%)**	257 **(49%)**	355 **(51%)**	361 **(51%)**
eGFR ≥ 60 to < 90, n (%)	270 **(52%)**	259 **(49%)**	245 **(47%)**	312 **(45%)**	300 **(43%)**
eGFR < 60, n (%)	22 **(4%)**	25 **(5%)**	24 **(5%)**	32 **(5%)**	42 **(6%)**

eGFR 60 to < 90 Subgroup: Achieves Meaningful A1C Reduction



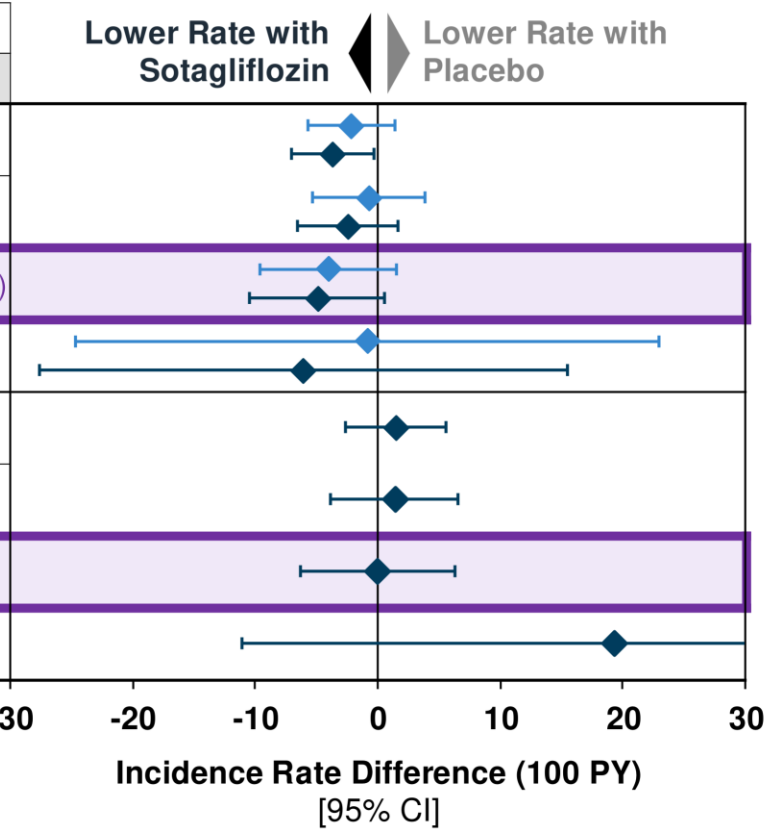
eGFR 60 to < 90 Subgroup: Reduction in Level 2 Hypoglycemia



Level 2 hypoglycemia = hypoglycemia events with blood glucose levels ≤ 55 mg/dL

eGFR 60 to < 90 Subgroup: No Increased Risk of Severe Hypoglycemia

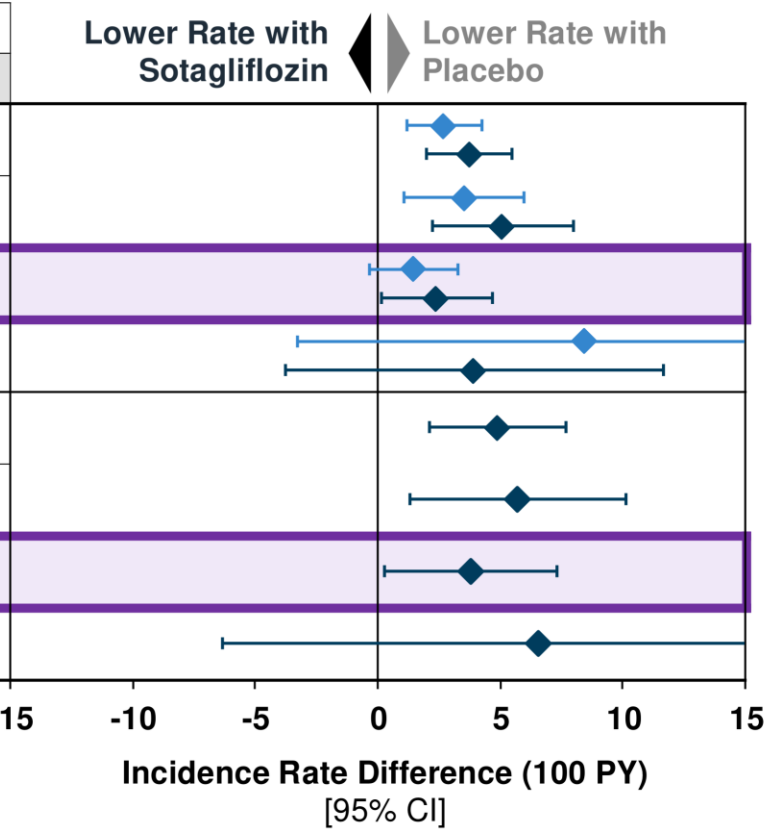
Positively Adjudicated Level 3 (Severe) Hypoglycemia		EAIR per 100 PY (n/N) 200 mg	400 mg	Placebo
Pooled Studies 309/310 (52 Weeks)	Overall Population	**6.5** (30/524)	**5.0** (23/525)	**8.6** (39/526)
	eGFR ≥ 90	**5.5** (11/232)	**3.7** (8/241)	**6.2** (14/257)
	eGFR ≥ 60 to < 90	**6.7** (16/270)	**5.8** (13/259)	**10.7** (22/245)
	eGFR < 60	**14.4** (3/22)	**9.2** (2/25)	**15.3** (3/24)
Study 312 (24 Weeks)	Overall Population		**7.2** (21/699)	**5.7** (17/703)
	eGFR ≥ 90		**6.0** (9/355)	**4.6** (7/361)
	eGFR ≥ 60 to < 90		**6.9** (9/312)	**6.9** (9/300)
	eGFR < 60		**25.0** (3/32)	**5.7** (1/42)



EAIR = Exposure-adjusted incidence rate

eGFR 60 to < 90 Subgroup: Increased Risk of DKA, Lowest Among eGFR Subgroups

Positively Adjudicated DKA		EAIR per 100 PY (n/N) 200 mg	400 mg	Placebo
Pooled Studies 309/310 (52 Weeks)	Overall Population	**2.9** (15/524)	**3.9** (20/525)	**0.2** (1/526)
	eGFR ≥ 90	**3.5** (8/232)	**5.1** (12/241)	**0** (0/257)
	eGFR ≥ 60 to < 90	**1.9** (5/270)	**2.8** (7/259)	**0.4** (1/245)
	eGFR < 60	**8.8** (2/22)	**4.1** (1/25)	**0** (0/24)
Study 312 (24 Weeks)	Overall Population		**6.0** (21/699)	**1.1** (4/703)
	eGFR ≥ 90		**7.3** (13/355)	**1.7** (3/361)
	eGFR ≥ 60 to < 90		**4.4** (7/312)	**0.6** (1/300)
	eGFR < 60		**6.6** (1/32)	**0** (0/42)



EAIR = Exposure-adjusted incidence rate

eGFR 60 to < 90 Subgroup has High Unmet Need and Removes Uncertainties in Patients with eGFR < 60

- Meaningful A1C reductions
- Reduction in Level 2 hypoglycemia events
- No increased rate of Level 3 (Severe) hypoglycemia
- DKA rate lowest among subgroups evaluated and lower than overall population

Planned Patient Selection, Education and Risk Minimization Activities to Ensure Safe Use of Sotagliflozin

Patient Selection is First Step in Minimizing Potential Risk with Sotagliflozin in T1D-CKD Population

Patient history informs physicians on appropriate patient selection

- ✓ Normal baseline blood beta hydroxybutyrate (BHB) levels
- ✓ Ability to maintain prescribed insulin management regimen
- ✓ Willingness to self-monitor
- ✓ Follows “sick day” rules
- ✓ No recurrent DKA within 12 months

“Sick Day” rules when ill or symptoms of DKA: Continue taking insulin and diabetes pills as usual. Test blood sugar every 4 hours. Measure ketones and blood beta hydroxybutyrate (BHB) levels when suspect hyperglycemia. Stay hydrated, drinking plenty of water. Treat diarrhea or vomiting to prevent dehydration.

Distribution and Education Plan for Patient and Physicians to Facilitate Safe Use of Sotagliflozin

Patient Materials

- ✓ Medication guide
- ✓ STICH guidelines[1]
- ✓ Patient wallet card
- ✓ Patient tear sheet
- ✓ Educational videos

Physician Materials

- ✓ Medication guide
- ✓ Dear HCP letters
- ✓ Dear pharmacist letter
- ✓ Scientific exchange

1. **STICH: ST**op using SGLT2 inhibitors until ketones are back to baseline; **I**nject short-acting insulin; **C**onsume 30-60 grams of carbohydrates; and **H**ydrate with 8-16 oz of fluid

Results in Patients with Diabetes and More Advanced Kidney Disease

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SCORED Study

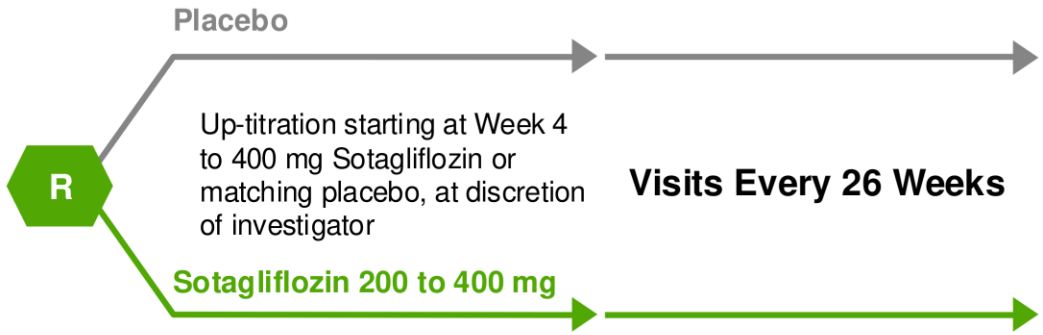
Long-Term Clinical Benefits of Sotagliflozin – T2D-CKD and Other CV Risk Factors

T2D-CKD SCORED: Phase 3, Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study

SCORED
N = 10,584

Key Inclusion Criteria

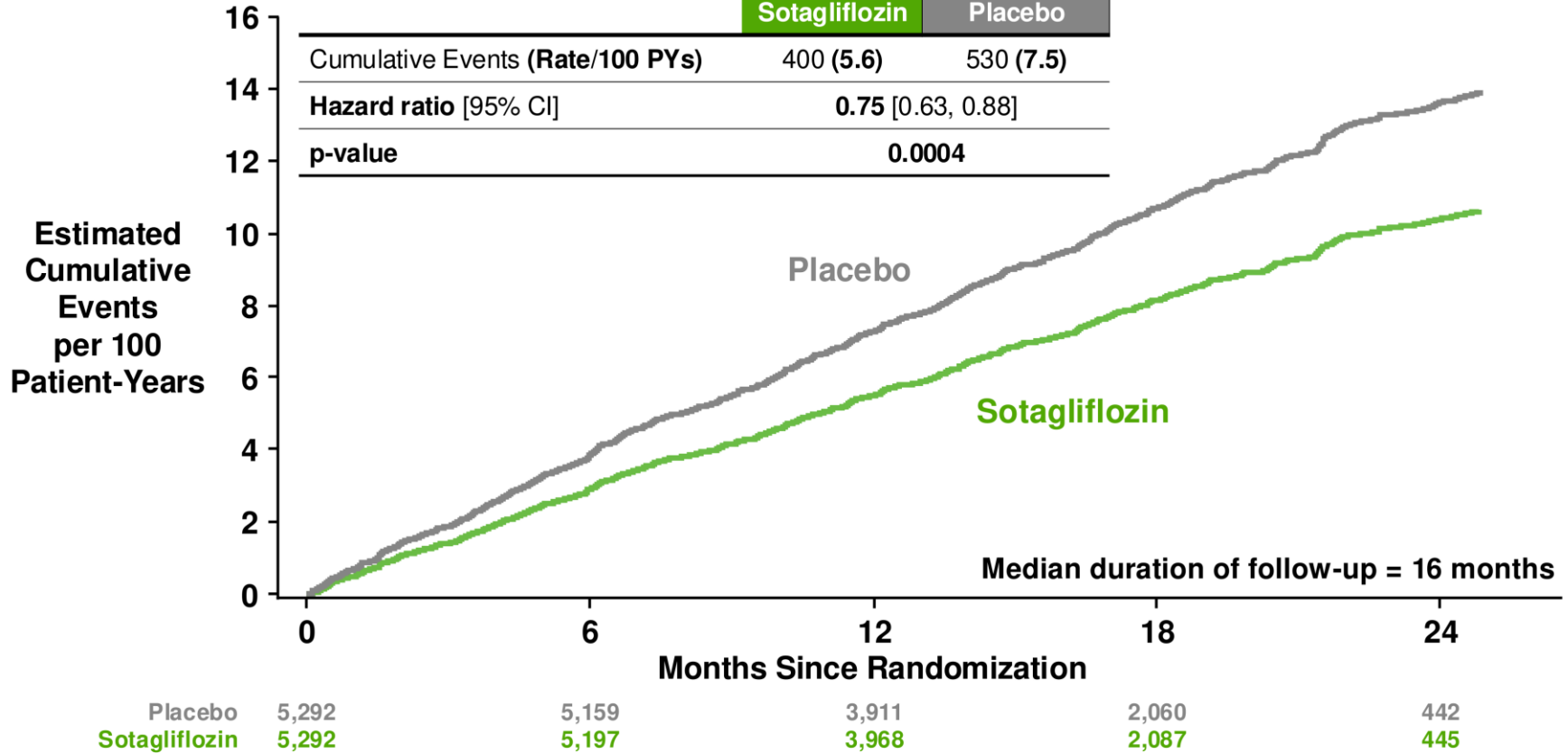
- Adults with T2D
- CKD defined as eGFR 25-60 mL/min/1.73m^2 regardless of UACR
- ≥ 1 major CV risk factor, or age ≥ 55 years with ≥ 2 minor CV risk factors



Primary Endpoint: Composite of total occurrence of cardiovascular death, hospitalization for heart failure, and urgent visit for heart failure

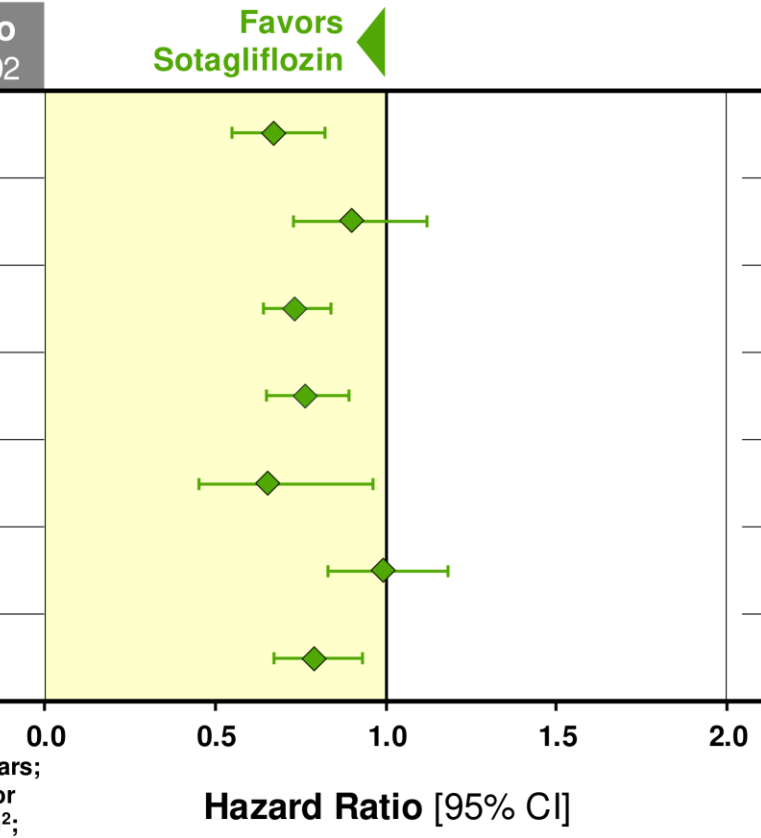
T2D-CKD SCORED: 25% Reduction in Risk of CV Death and HF-Related Events With Sotagliflozin

	Sotagliflozin	Placebo
Cumulative Events **(Rate/100 PYs)**	400 **(5.6)**	530 **(7.5)**
Hazard ratio [95% CI]	**0.75** [0.63, 0.88]	
p-value	**0.0004**	



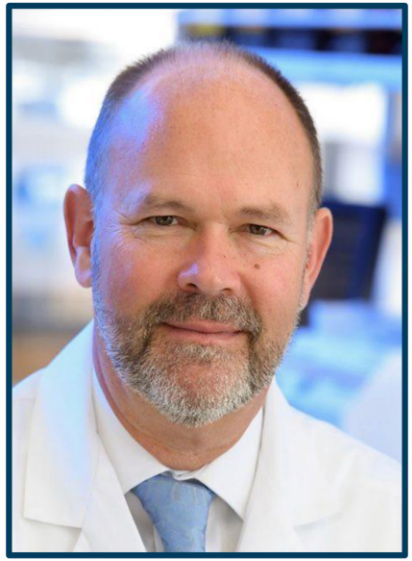
T2D-CKD SCORED: Consistent Benefit of Sotagliflozin Across Hierarchically Tested Secondary Endpoints

	Sotagliflozin N = 5,292	Placebo N = 5,292	p-value
HHF and UVHF, E/100 PY	3.5	5.1	0.0001
CV death, %	2.9	3.2	0.36
CV death, HHF, non-fatal MI, and non-fatal stroke, E/100 PY	7.1	9.6	< 0.0001*
CV death, HHF, UVHF, or HF while hospitalized, E/100 PY	6.4	8.3	0.0005*
eGFR↓ ≥ 50% or kidney failure, %	0.8	1.2	0.0303*
All-cause mortality, %	4.6	4.6	0.93*
CV death, non-fatal MI, and non-fatal stroke, E/100 PY	4.3	5.4	0.0047*



* Nominal p-value

CI: confidence interval; CV: cardiovascular; E/100 PY: event rate per 100 patient-years; eGFR: estimated glomerular filtration rate; HF: heart failure; HHF: hospitalization for HR; Kidney failure: chronic dialysis, kidney transplant, or eGFR < 15 mL/min/1.73m^2; MI: myocardial infarction; UVHF: urgent visit for heart failure



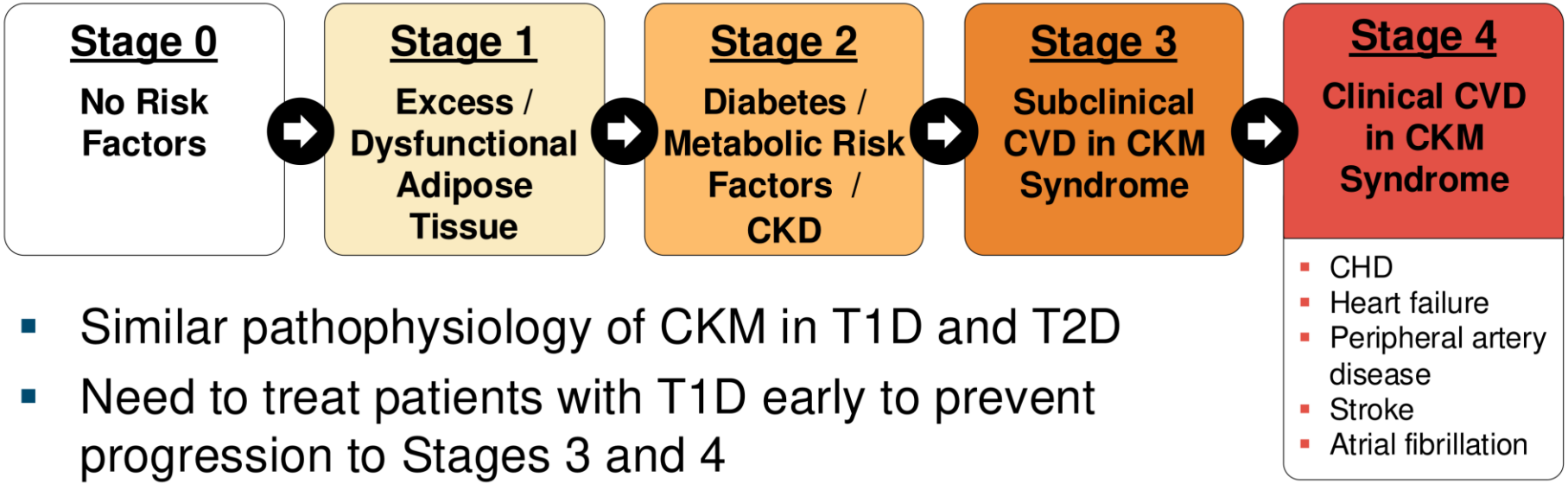
T1D-CKD Management, Risk Management, Patient Education

Richard Pratley, MD

Medical Director at the AdventHealth Diabetes Institute
Senior Investigator, Diabetes Program Lead at the Translational Research Institute

Most People with Diabetic Kidney Disease Die of Heart Failure or Atherosclerotic CV Events Prior to ESKD

Progression of Cardiovascular-Kidney-Metabolic (CKM) Syndrome



- Similar pathophysiology of CKM in T1D and T2D
- Need to treat patients with T1D early to prevent progression to Stages 3 and 4

Image adapted from American Heart Association's Figure 2. Stages of CKM syndrome

Patients with T1D and CKD Have Limited Therapeutic Options

- ADA / KDIGO recommendations offer many more therapy options for T2D patients and CKD

Target	T2D Therapies	T1D Therapies
Glucose	Insulin Metformin Sulfonylureas Glucagon-like peptide-1 receptor agonist (GLP-1RA) Sodium–glucose cotransporter-2 inhibitor (SGLT2i)	Insulin Pramlintide
Kidney	Renin-angiotensin system inhibitor (RAS) SGLT2i Nonsteroidal mineralocorticoid receptor antagonist	RAS
CV / HF	Statins/LLD, RAS, calcium channel blocker, diuretic SGLT2i GLP-1RA	Statins/LLD, RAS, calcium channel blocker, diuretic

Need to Avoid Risks Caused by Poor Glycemic Control

- Every 1% increase in A1C associated with
  - 54% increase in 1st MACE and 77% for subsequent events[1]
  - > 3-fold increase in HF risk[1]
  - > 2.5-fold increase in CV death[1]
  - 2-fold increase in kidney outcomes[2]
  - > 2-fold increase in retinopathy[3]

1. Bebu, 2020; 2. Perkins, 2019; 3. Hainsworth, 2019

Patients with T1D-CKD Gain Clinically Meaningful Improvements in Multiple CKM Endpoints with Sotagliflozin

- Improvement in glycemic control
  - Improved A1C
  - Improved time in range
  - No increase in hypoglycemia
- Clinically meaningful reductions in body weight
- Potential benefits on long-term kidney and CV outcomes
  - Demonstrated evidence of benefit in patients with T2D based on SCORED

CKM: Cardiovascular-Kidney-Metabolic

Careful Selection of Patients Helps Mitigate Glucose-Related Risks When Adding Therapies

- Patients with T1D-CKD have established history that informs clinicians on level of engagement
- Successful patients:
  - Able to maintain prescribed insulin regimen
  - Monitor and manage glucose excursions
  - Effectively use diabetes devices (e.g., CGM, insulin pump)
  - Ketone measurements for suspected DKA
  - Willing to take additional steps to improve glycemic control
- Glycemic targets are less aggressive in those who can't recognize or take steps to mitigate glucose-related risks

Sotagliflozin Addresses the Urgent Need for Therapies for Patients with T1D and CKD

- Improves A1C
  - Improves time in range without increasing severe hypoglycemia
- Increases DKA risk
  - Careful patient selection and education is very important to lessen risk
- Potential CKD benefits from improved glycemic control

Patients engaged in their diabetes management, and willing to initiate new treatments should have access to Sotagliflozin

Conclusion

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Sotagliflozin Proposed Indication Intended to Help T1D Patients with Highest Risk

Adjunct to insulin therapy to improve glycemic control in adults with T1D and CKD

Positive Sotagliflozin Benefit-Risk in Patients with High Unmet Need (T1D-CKD and eGFR 60 to < 90 Subgroups)

Overall Population

- Statistically significant A1C Reductions
- Reduction in Level 2 hypoglycemia events
- No Increased risk of Level 3 (severe) hypoglycemia
- Increased risk of DKA

2019 EMDAC Voted 8-8 Benefit-Risk

T1D-CKD

- Consistent efficacy and safety profile compared to overall population
- Most advanced CKD; population with greatest unmet need
  - Incremental benefits from similar efficacy
- SCORED supports potential long-term benefit on clinical outcomes

Improved Benefit-Risk vs Overall Population

eGFR 60 to < 90

- Removes uncertainties in patients with eGFR < 60
- Retains mild to moderate risk population that needs to slow disease progression

Improved Benefit-Risk vs Overall Population

Sotagliflozin to Improve Glycemic Control in Adults with Type 1 Diabetes (T1D) Mellitus and Chronic Kidney Disease (CKD)

October 31, 2024

Endocrinologic and Metabolic Drugs Advisory Committee

Lexicon Pharmaceuticals, Inc.

Back Up Slides Shown

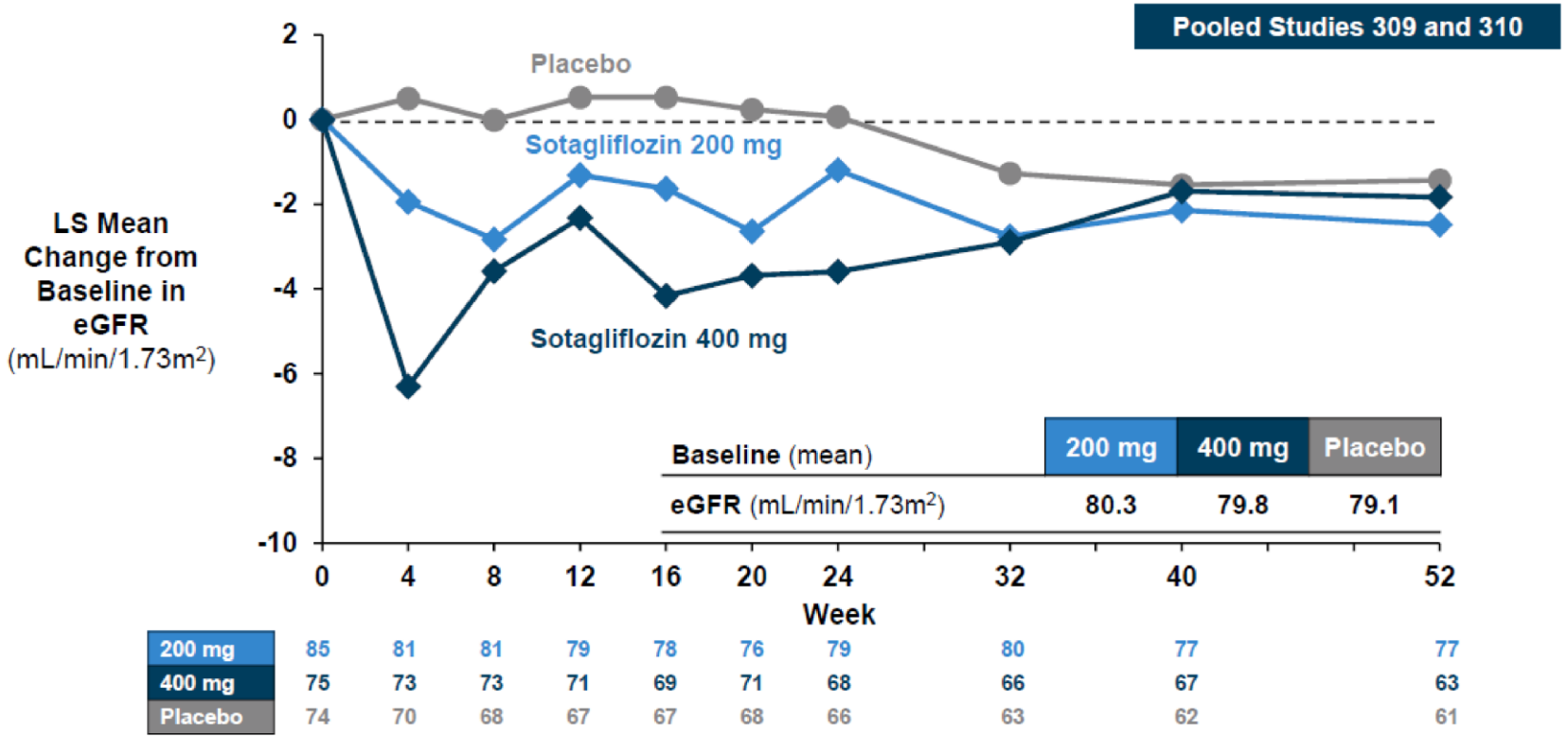
T1D-CKD: Investigator-Reported and Positively Adjudicated DKA Events

Patients, % (n)	Pooled Studies 309 and 310			Study 312		Pooled Studies 309 and 310			Study 312	
	200 mg N = 85	400 mg N = 75	Placebo N = 74	400 mg N = 114	Placebo N = 110	200 mg N = 270	400 mg N = 259	Placebo N = 245	400 mg N = 312	Placebo N = 300
Investigator Reported DKA / metabolic acidosis	**6%** (5)	**7%** (5)	**3%** (2)	**4%** (5)	**3%** (3)	**4%** (12)	**7%** (17)	**1%** (3)	**3%** (9)	**0.3%** (1)
Positively adjudicated DKA	**5%** (4)	**3%** (2)	**1%** (1)	**3%** (3)	**1%** (1)	**2%** (5)	**3%** (7)	**0.4%** (1)	**2%** (7)	**0.3%** (1)

Positively Adjudicated DKA: Summary of Potential Possible Risk Factors, Pooled 309/310/312

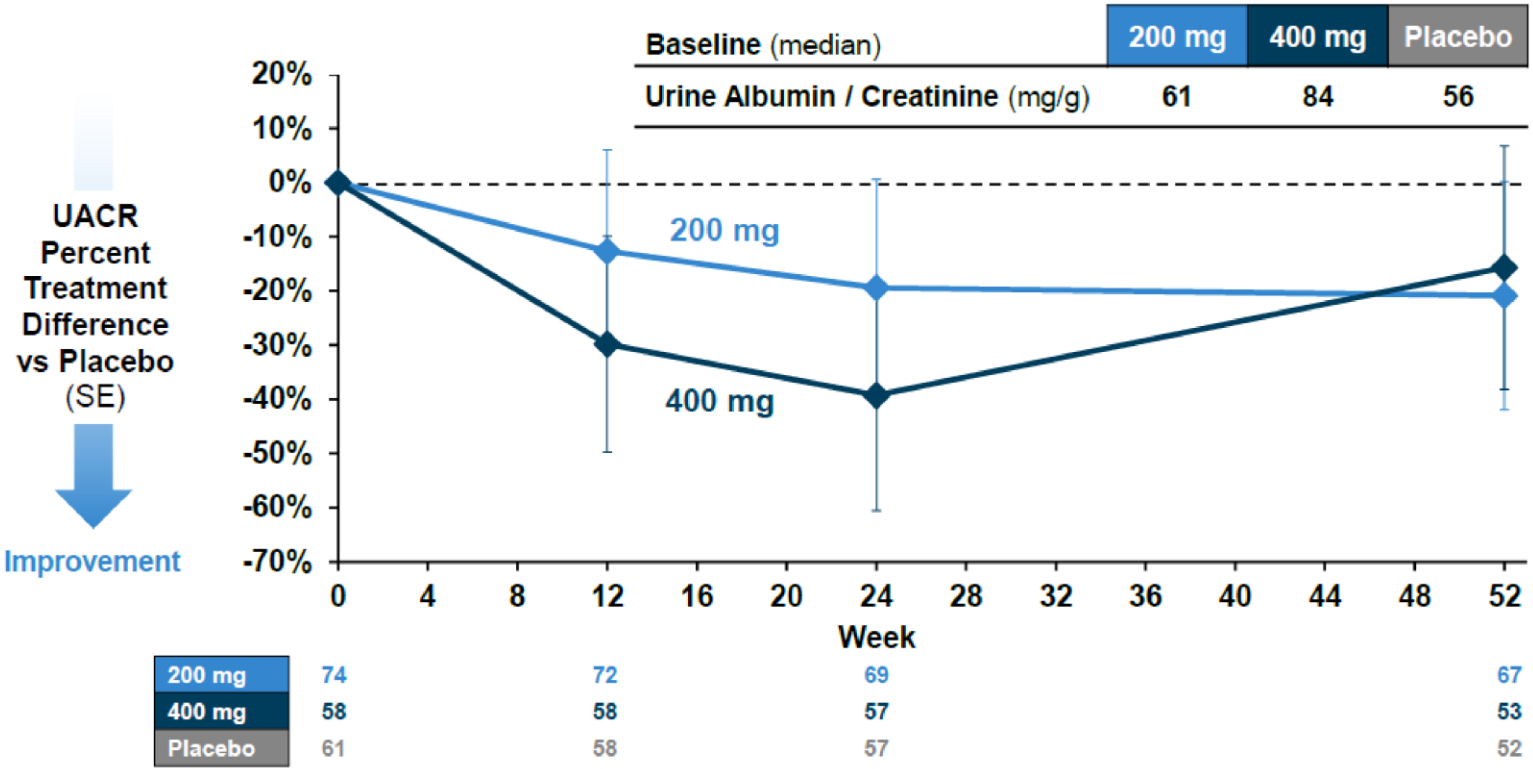
	T1D-CKD N = 274	T1D eGFR 60 to < 90 N = 841
Sotagliflozin treated - total DKA	9	19
Infection	3	5
Illness	6	4
Insulin issue	0	4
Other	0	2
None identified	0	4

Figure 36: eGFR Change from Baseline through Week 52 in the T1D-CKD Population in Pooled Studies 309 and 310



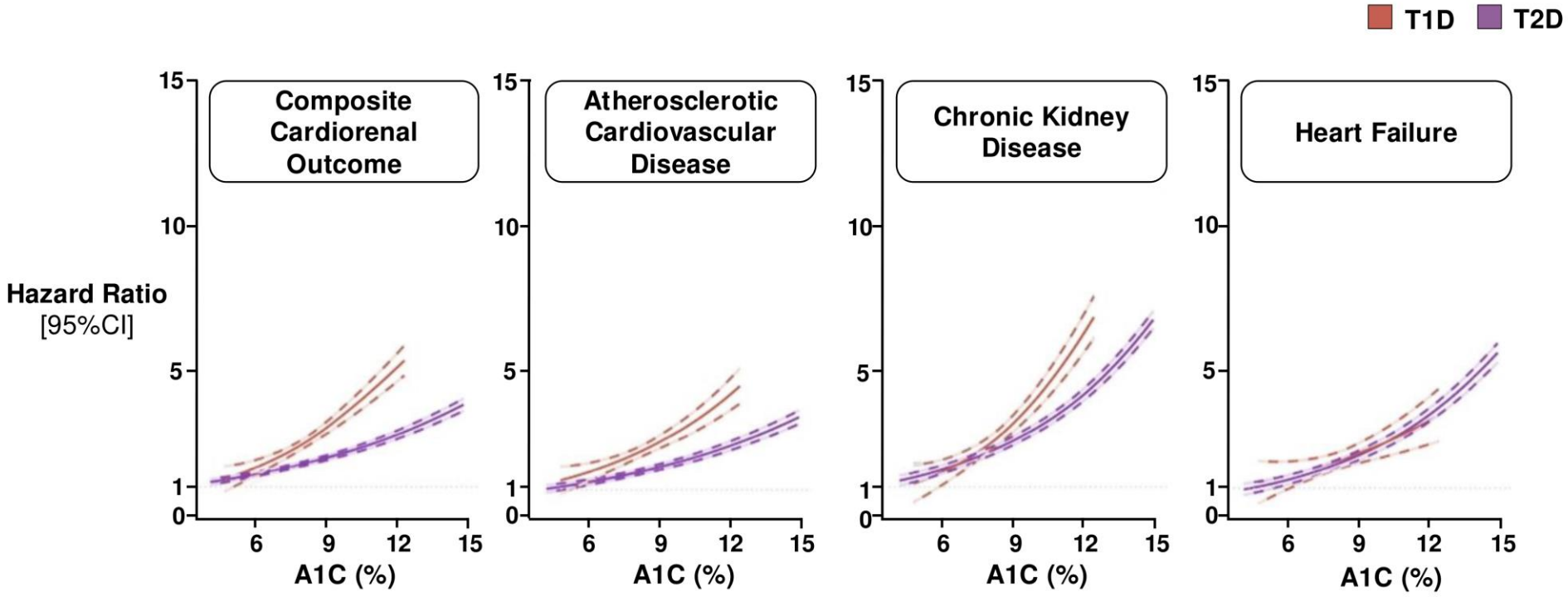
CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; LS: least squares; T1D: type 1 diabetes mellitus

Figure 37: Urine Albumin-to-Creatinine Ratio Change from Baseline through Week 52 in the T1D-CKD Population with Baseline UACR ≥30 mg/g in Pooled Studies 309 and 310



CKD: chronic kidney disease; SE: standard error; T1D: type 1 diabetes mellitus; UACR: urine albumin-to-creatinine ratio

Negative Cardiorenal Outcomes in Adults are Equal or Greater in T1D than T2D



Ostrominski, 2024

Baseline Characteristics Across T2D-CKD SCORED and T1D-CKD Pooled Studies 309 / 310, and 312

Mean	T2D-CKD SCORED[1] Sotagliflozin N = 5,292	T2D-CKD SCORED[1] Placebo N = 5,292	T1D-CKD Subgroup Pooled Studies 309 / 310 Sotagliflozin N = 160	T1D-CKD Subgroup Pooled Studies 309 / 310 Placebo N = 74	T1D-CKD Subgroup Study 312 Sotagliflozin N = 114	T1D-CKD Subgroup Study 312 Placebo N = 110
Age (years)	68	68	47	49	48	47
Female (%)	44%	46%	49%	54%	47%	50%
BMI (kg/m^2)	33	32	29	29	29	28
Diabetes Duration (years)	17	17	26	26	24	23
A1C (%)	8.7	8.7	7.8	7.8	8.3	8.7
SBP (mmHg)	138	138	127	128	125	128
eGFR (mL/min/1.73 m^2)	44	44	80	79	82	80
Median UACR (mg/g)	80	84	54	49	60	61
ACEi (%)	38%	39%	33%	47%	38%	38%
ARB (%)	50%	48%	19%	22%	20%	19%

1. Bhatt, 2021