Sotagliflozin as an Adjunct to Insulin for Type 1 Diabetes

January 17, 2019

Sanofi / Lexicon Pharmaceuticals

Endocrinologic and Metabolic Drugs Advisory Committee

Introduction

Rene Belder, MD

Vice President

Diabetes and Cardiovascular Clinical Development

Sanofi

Insulin: Life-Saving But Difficult to Dose Correctly

Underdosing

- ↑ Hyperglycemia
- ↑ Diabetic ketoacidosis (DKA)

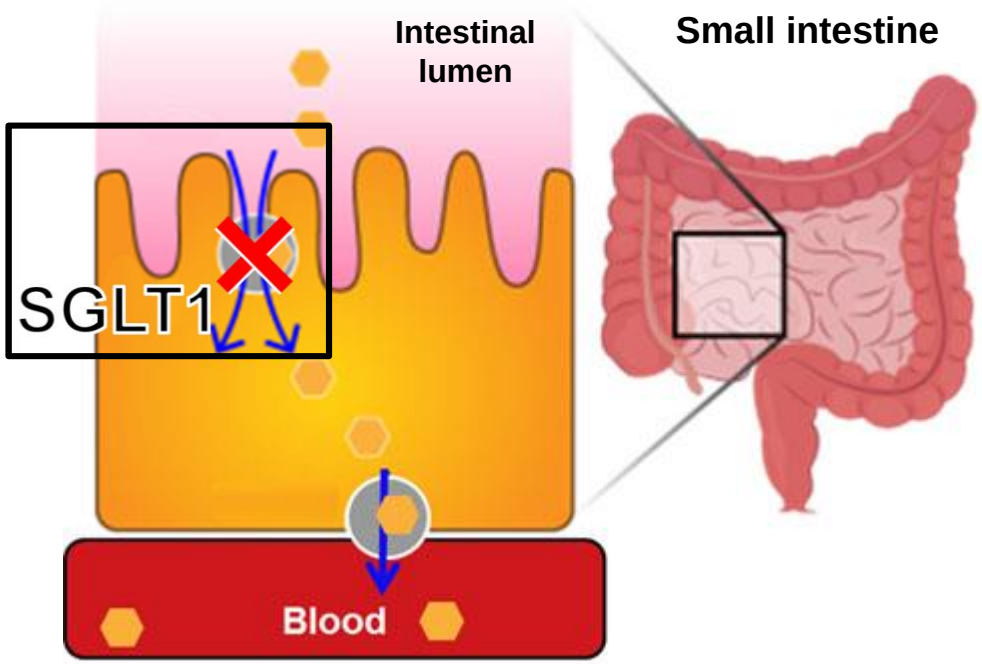
Overdosing

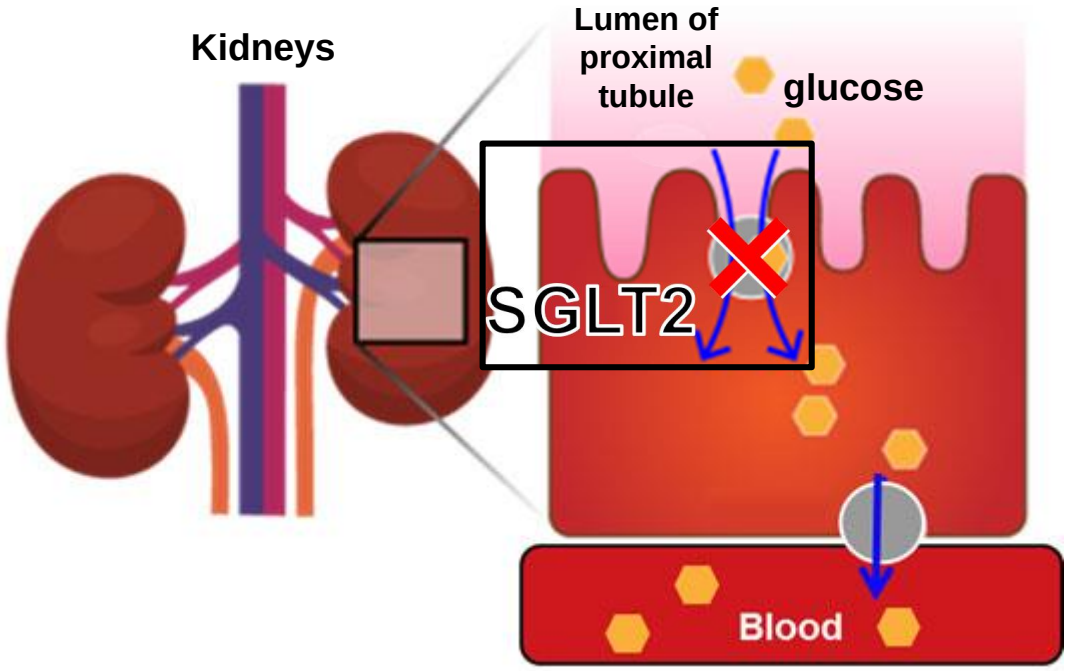
- ↑ Hypoglycemia
- ↑ Weight gain

Imprecision

- ↑ Glucose Variability
- ↑ Distress

Sotagliflozin: Dual Inhibitor of SGLT1 and SGLT2





- SGLT1 inhibition blunts and delays glucose absorption and reduces postprandial glucose (PPG) excursions[1]
- SGLT2 inhibition reduces glucose reabsorption, lowering blood glucose[2]

1. Dobbins RL et al. 2015; 2. Rieg T et al. 2014

Sotagliflozin Proposed Indication and Dosing

- Sotagliflozin, an inhibitor of the sodium-dependent glucose co-transporters (SGLT) 1 and SGLT2, is indicated as an adjunct to insulin therapy to improve glycemic control in adults with type 1 diabetes mellitus who have failed to achieve desired glycemic control despite optimal insulin therapy.
- Recommended dose
  - 200 mg orally, once daily before first meal
  - Dose may be increased to 400 mg in patients who tolerate 200 mg and need additional glycemic control

Sotagliflozin Clinical Development Program Largest to Date in Adults with T1D

- 30 clinical studies including 4,010 adults

Phase 3 Study	Total Duration	N
309 (North America)	52 weeks	793
310 (Europe and Israel)	52 weeks	782
312 (Global)	24 weeks	1,405

Sotagliflozin – Effective Adjunct to Insulin Therapy

- Provides statistically significant and clinically important reductions in A1c
- Improves glycemic control with lower risk of hypoglycemia
- Favorable effects on other glycemic endpoints
  - Time in range, PPG, fasting plasma glucose (FPG)
- Improves cardiovascular risk factors
  - Body weight, blood pressure
- Decreases disease burden

Sotagliflozin – Safety Profile

- Well-tolerated
- > 80% of patients completing 52 weeks
- Lower risk of hypoglycemia than insulin alone
- Higher risk of diabetic ketoacidosis (DKA)

DKA Known Risk in T1D

- Occurs with absolute insulin deficiency (e.g. missed doses) or relative insulin deficiency (e.g. stress, illness)
  - Increases glucose levels
  - Metabolic shift to fat burning
  - Increase of ketones or ketosis and potentially DKA
- DKA risk mitigation and management already standard of care

SGLT2 Inhibition Increases Risk of DKA in T1D

- DKA, on or off SGLT2, caused by same mechanism
  - Absolute or relative insulin deficiency
- Traditionally recognized through symptoms and hyperglycemia
- SGLT2 inhibitors lower glucose levels independent of insulin
  - Hyperglycemia not as reliable an indicator of DKA
- Important to measure and rely on ketones

Proposed Risk Management Program to Reduce Risk of DKA

- Based on current practice guidelines
  - Patient selection, ketone monitoring, insulin management, recognizing at-risk situations, and use of sick-day rules
- Communicate risk of DKA to HCPs and patients
  - Educational materials and patient leaflets

Agenda

Unmet Medical Need in Adults with Type 1 Diabetes	**Steven Edelman, MD** Clinical Professor of Medicine UC San Diego
Clinical Efficacy Results	**Pablo Lapuerta, MD** Executive Vice President and Chief Medical Officer Lexicon Pharmaceuticals
Clinical Safety Results	**Klaus Henning Jensen, MD** Head of Diabetes, Cardiovascular and Metabolism Development Sanofi
Clinical Perspective	**Juan Pablo Frias, MD** Medical Director and Principal Investigator National Research Institute

Additional Experts

Diabetic Ketoacidosis	**Ketan Dhatariya, MBBS, MSc, MD, MS, FRCP, PhD** Consultant Physician Norfolk and Norwich University Hospitals NHS Foundation Trust U.K.
Biostatistics	**LJ Wei, PhD** Professor of Biostatistics Harvard T.H. Chan School of Public Health
Cardiology	**Darren McGuire, MD** Professor UT Southwestern Medical Center
Principal Investigator European Trial	**Thomas Danne, MD** Diabetes Center “Auf der Bult“, Hannover Medical School, Germany
Translational Medicine	**Ele Ferrannini, MD, PhD** Professor of Internal Medicine University of Pisa
Pharmacoepidemiology	**Elizabeth Andrews, PhD** Vice President, Pharmacoepidemiology and Risk Management RTI Health Solutions

Unmet Medical Needs in Adults with Type 1 Diabetes

Steven Edelman, MD

Clinical Professor of Medicine

University of California San Diego School of Medicine

Founder and Director, Taking Control of Your Diabetes, a 501(c)3 Not-for-Profit Organization

Type 1 Very Different from Type 2 Diabetes

- Etiology and treatment strategies
- Autoimmune disease
- Absolute insulin deficiency
- Require intensive insulin therapy
- Glycemic unmet needs go far beyond A1c

Discovery of Insulin Significantly Changed and Prolonged Lives of Patients with T1D

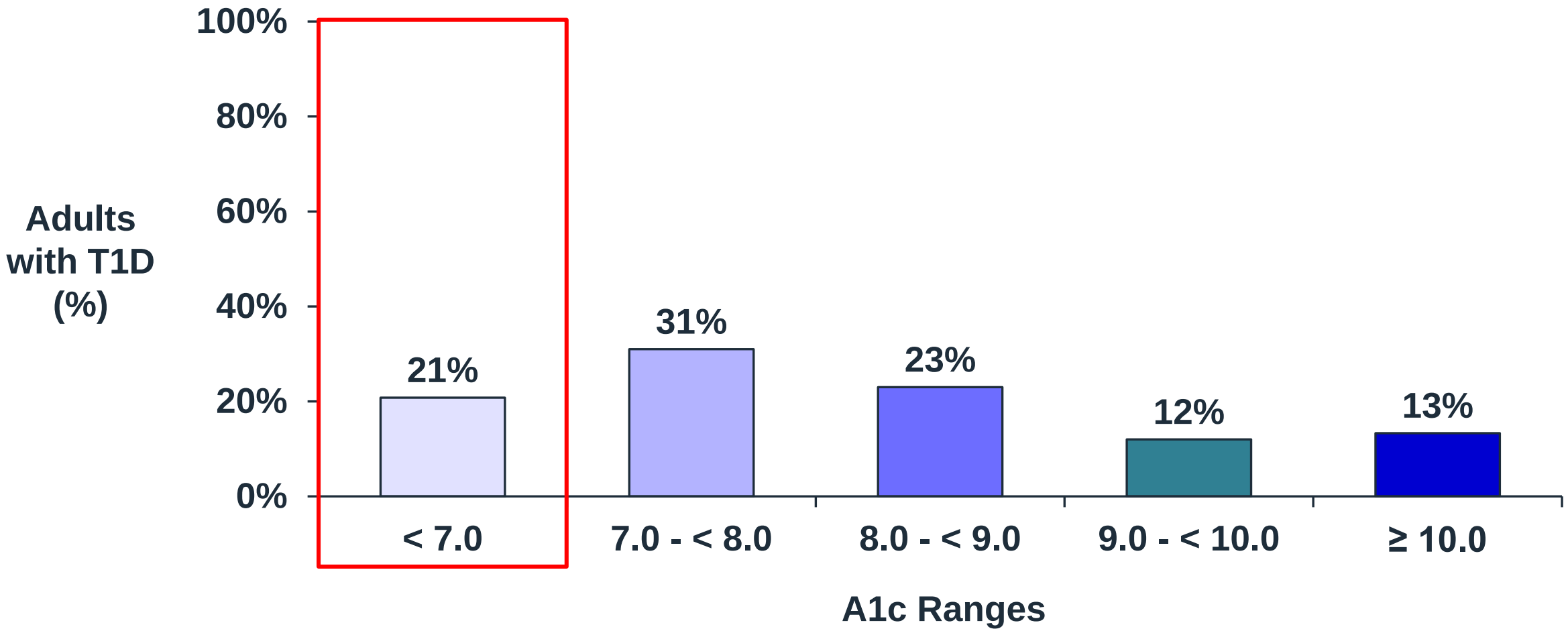
Ted Ryder Before Insulin

Ted Ryder 5 Months After Insulin

Limitations of Insulin Therapy

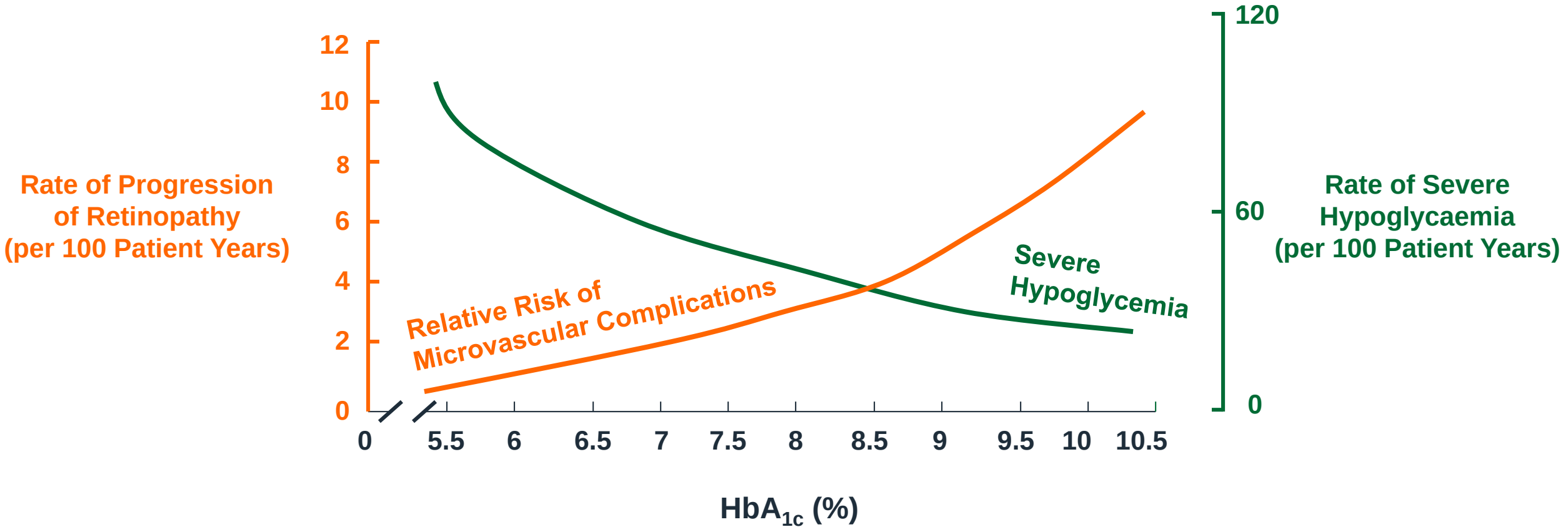
- Hypoglycemia
- Weight gain
  - Hypertension and other co-morbidities
  - Premature cardiovascular disease
- Insulin contributes to unpredictable swings in glucose values

Less than 1/4 of Patients with T1D Reach ADA Goal of A1c < 7.0%



Beck et al, 2012

Trade-Off Between Microvascular Complications and Hypoglycemia



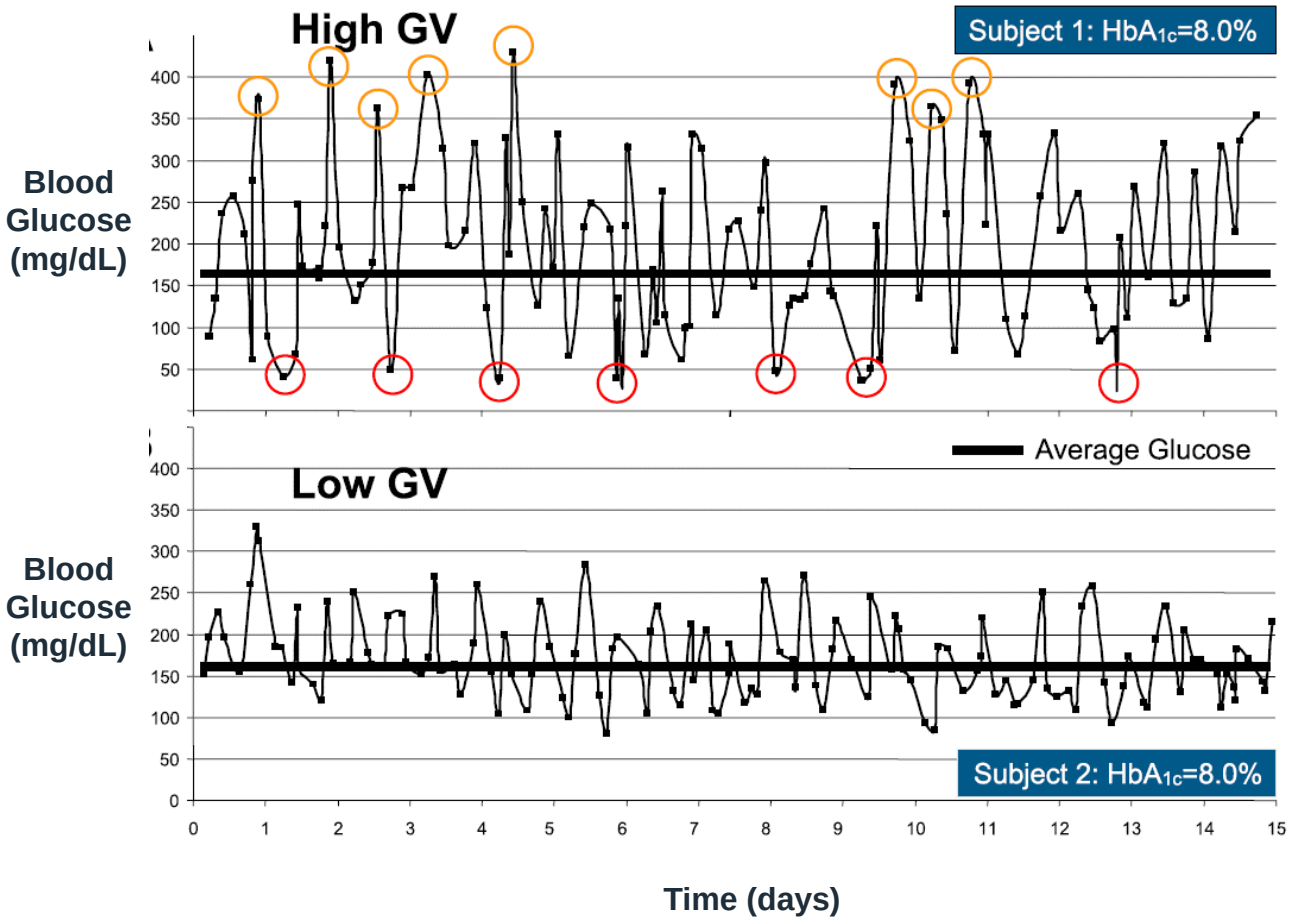
DCCT Research Group, 1993

A1c Gold Standard for Predicting Microvascular Complications

- Does not capture day-to-day patients' disease control
- Other glycemic indices better reflection of patient experience
  - Time in range (between 70 and 180 mg/dL)

Glucose Variability Has Important Impact on Patients with T1D

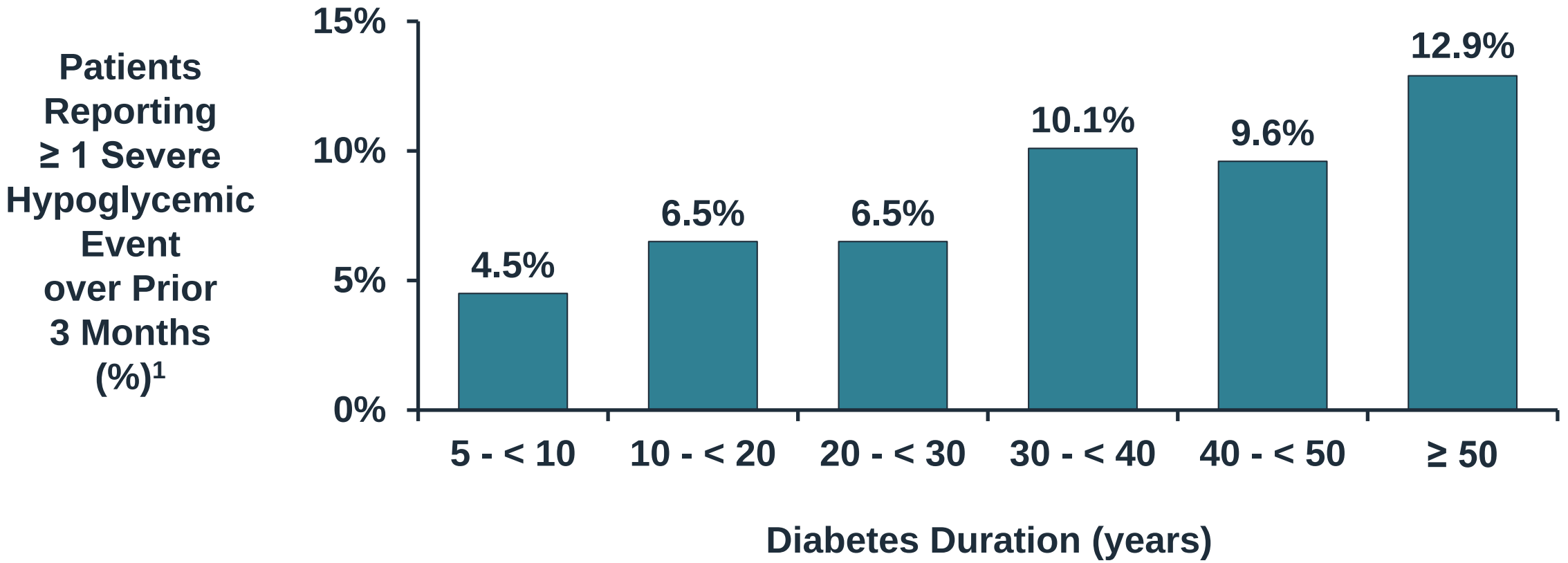
Fluctuations in Daily Glucose Levels in Two Different Patients[1]



- Measuring A1c alone gives no information on variability[1-4]
- Importance of avoiding extreme hyperglycemia and dangerous hypoglycemia
- Improvement in time in range significantly reduced retinopathy and nephropathy[5]

1. Kovatchev B et al, 2016; 2. Suh S et al, 2015; 3. Bergenstal RM, 2015; 4. Evans M et al, 2017; 5. Beck, 2018

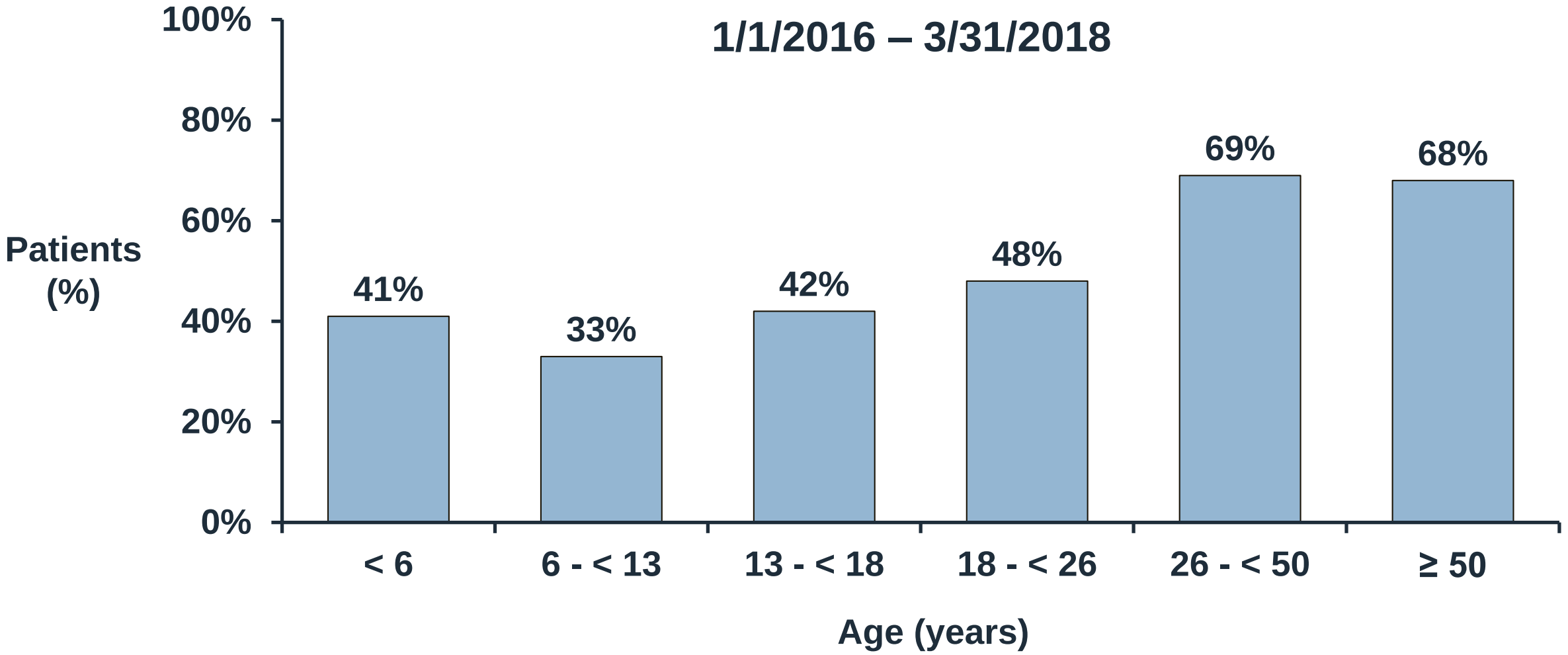
Severe Hypoglycemia in T1D



- Between 4% and 10% of deaths in T1D due to severe hypoglycemia[2]

1. The T1D Exchange Clinic Registry, 2018; 2. Seaquist E et al, 2012

More Patients with T1D Overweight and Obese



The T1D Exchange Clinic Registry, 2018

Increased Risk of Hypertension and Cardiovascular Disease in T1D Population

- ~3 times higher prevalence of hypertension[1]
- 10 times greater risk of cardiovascular disease[2]
- 4 times greater risk of hospitalization for heart failure[3]
- Cardiovascular disease leading cause of death[4]

1. Maahs DM et al, 2005; 2. de Ferranti SD et al, 2014; 3. Rosengren A et al, 2015; 4. Rawshani A et al, 2017

DKA – Known Severe Risk in T1D

- Patients with T1D, especially those on pumps, taught sick-day rules to mitigate and treat themselves
- Sick day rules to prevent ER visit or hospitalization
  - Enhanced monitoring
  - Early insulin dosing
  - Fluids and carbohydrates
- Incidence up to 5.1 per 100 patient years[1,2]

1. Bohn B et al, 2015; 2. Hoshina S et al, 2018

Unmet Needs in T1D

- Reaching A1c goal without hyperglycemia and hypoglycemia
- Reducing glycemic variability and improving time in range
- Controlling blood pressure and reducing heart disease
- Preventing and controlling weight gain
- High emotional and physical burden

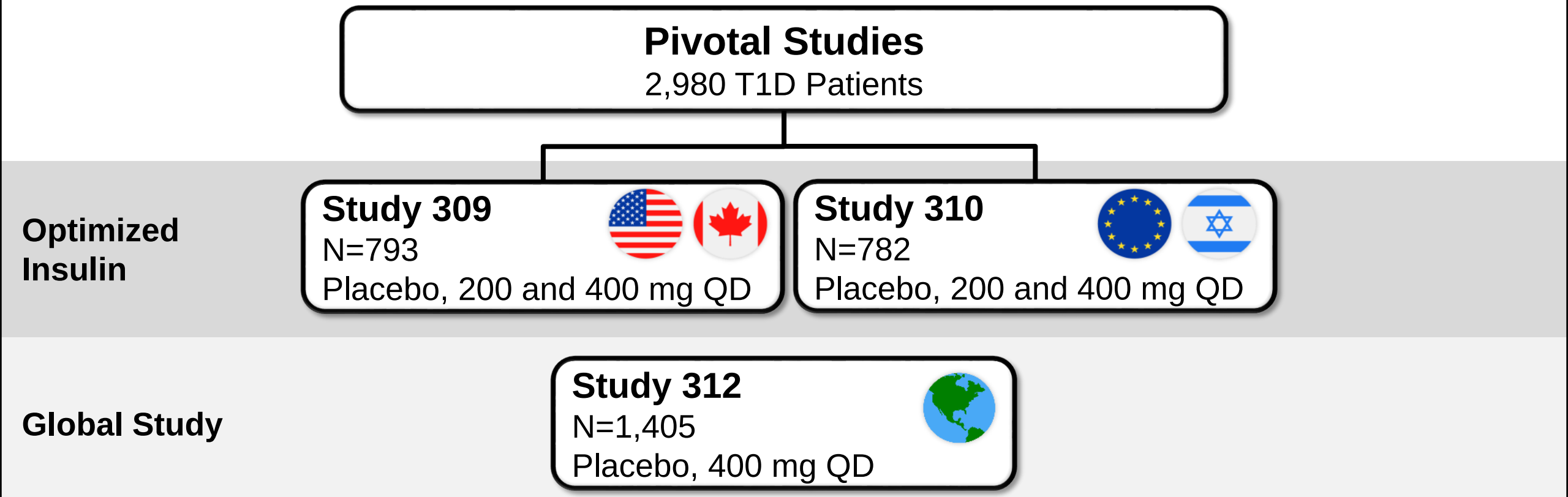
Clinical Efficacy Results

Pablo Lapuerta, MD

Executive Vice President and Chief Medical Officer

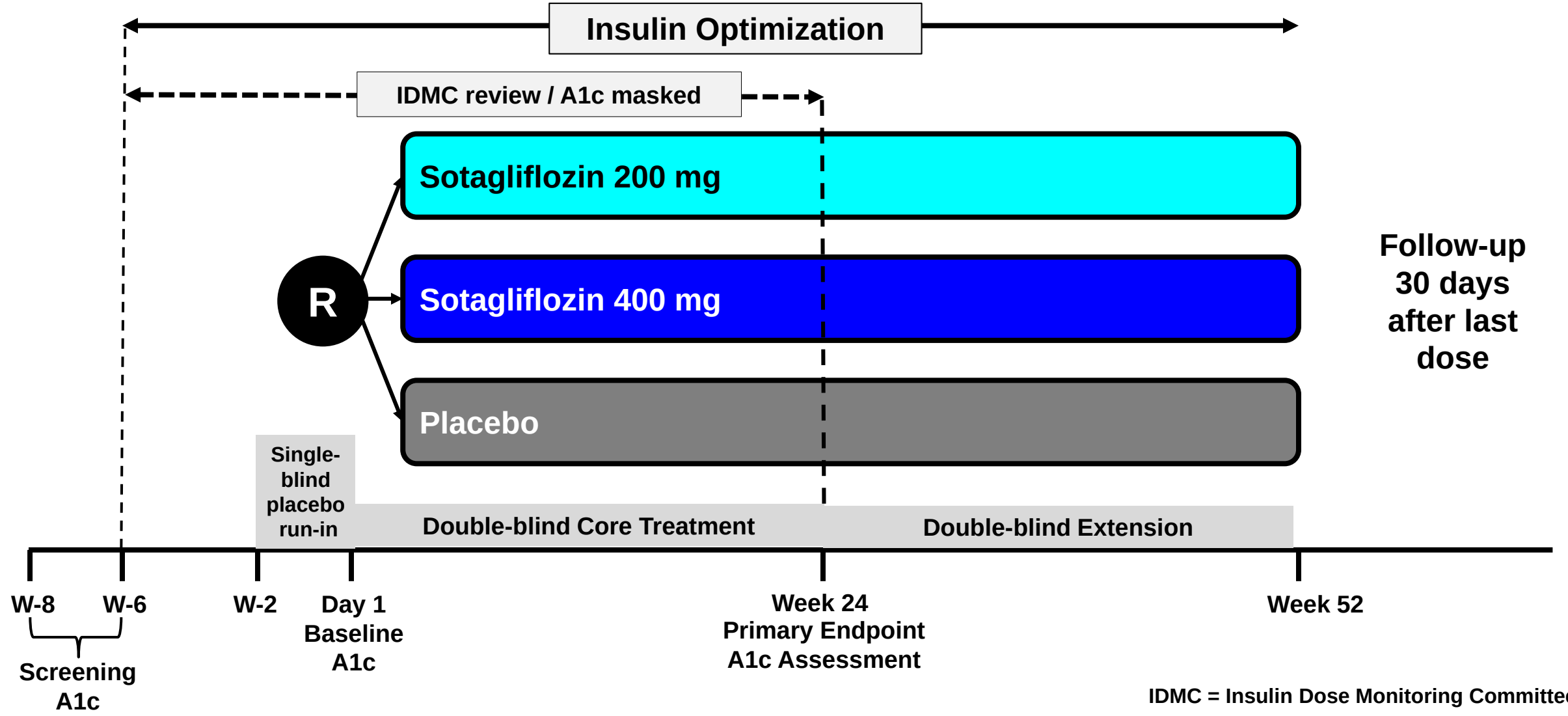
Lexicon Pharmaceuticals

Phase 3 Studies Support Sotagliflozin Proposed Indication



- Sotagliflozin QD added to insulin resulted in significant A1c reduction
  - Benefits beyond A1c
  - Not achieved with insulin alone

Studies 309 / 310: Clinical Design



IDMC = Insulin Dose Monitoring Committee

Studies 309 / 310: Key Inclusion Criteria

- ≥ 18 years
- Diagnosis of T1D ≥ 1 year prior to informed consent
- Screening A1c 7.0% to 11.0%
- Insulin pump or multiple daily injections (MDI) therapy
- History of DKA and severe hypoglycemia (SH) allowed
  - No DKA or SH in 1 month before screening
  - ≤ 2 DKA in past 6 months before screening

Studies 309 / 310: Primary and Secondary Endpoints

- Primary endpoint
  - Change from Baseline to Week 24 in A1c
- Secondary endpoints*
  - Net benefit at Week 24
    - Proportion of patients with A1c < 7.0% without SH or DKA
  - Body weight
  - Bolus insulin dose
  - FPG
  - PROs

*Alpha protected

Studies 309 / 310: Efficacy Results

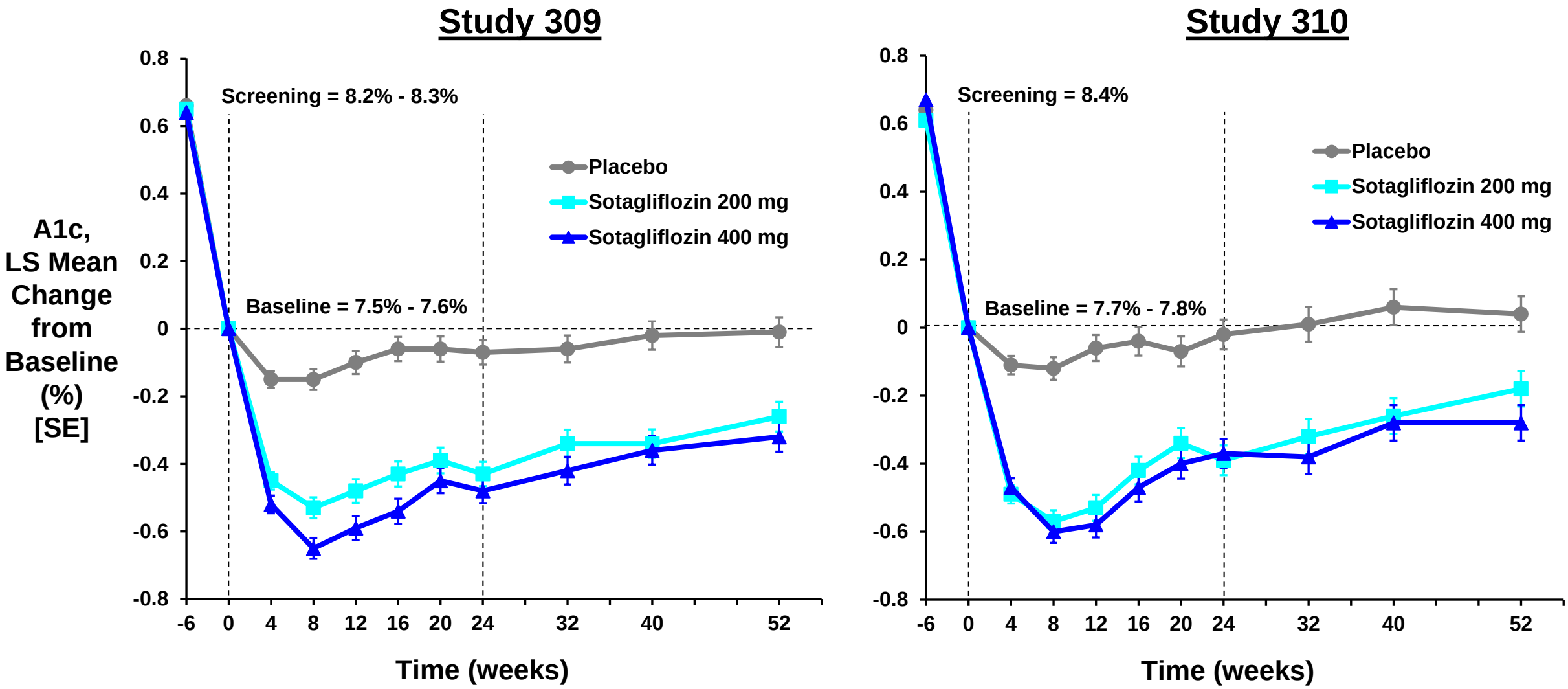
Studies 309 / 310: > 80% Completion Rate in All Groups

	Study 309			Study 310		
	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Randomized (N)	**268**	**263**	**262**	**258**	**261**	**263**
Core treatment discontinuations	**33 (12%)**	**23 (8.7%)**	**26 (9.9%)**	**22 (8.5%)**	**23 (8.8%)**	**23 (8.7%)**
Withdrawal by patient	18	14	13	18	14	9
AE	8	7	11	5	5	12
Lost to follow-up	1	1	1	1	1	0
Other	6	1	1	3	3	2
Long-term extension discontinuations	**17 (6.3%)**	**12 (4.6%)**	**15 (5.7%)**	**11 (4.3%)**	**13 (5.0%)**	**13 (4.9%)**
Withdrawal by patient	8	5	7	3	5	3
AE	3	6	6	4	5	6
Lost to follow-up	2	1	0	0	0	0
Other	4	0	2	4	3	4
Completed study	**218 (81%)**	**228 (87%)**	**221 (84%)**	**225 (87%)**	**226 (87%)**	**227 (86%)**

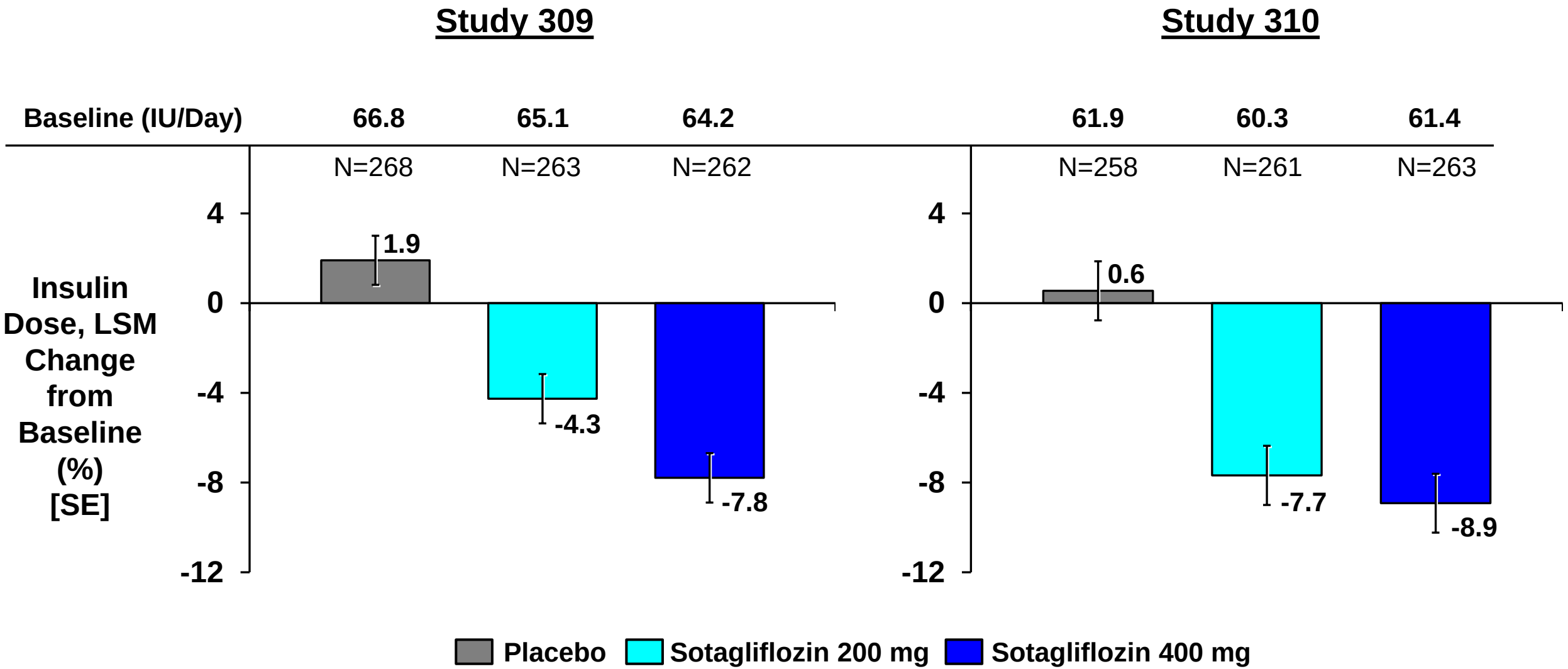
Studies 309 / 310: Demographics Balanced Between Groups and Representative of Patients with T1D

	Study 309			Study 310		
	Placebo N=268	Sotagliflozin 200 mg N=263	Sotagliflozin 400 mg N=262	Placebo N=258	Sotagliflozin 200 mg N=261	Sotagliflozin 400 mg N=263
Age, mean (years)	45	47	46	40	42	42
Race						
White	91%	92%	94%	97%	97%	95%
Black / African-American	3%	4%	3%	< 1%	0	0
Other	6%	4%	3%	3%	3%	5%
Sex, female	49%	52%	54%	48%	47%	49%
Body weight, mean (kg)	87	87	87	81	82	82
BMI, mean (kg/m^2)	30	30	30	28	28	28

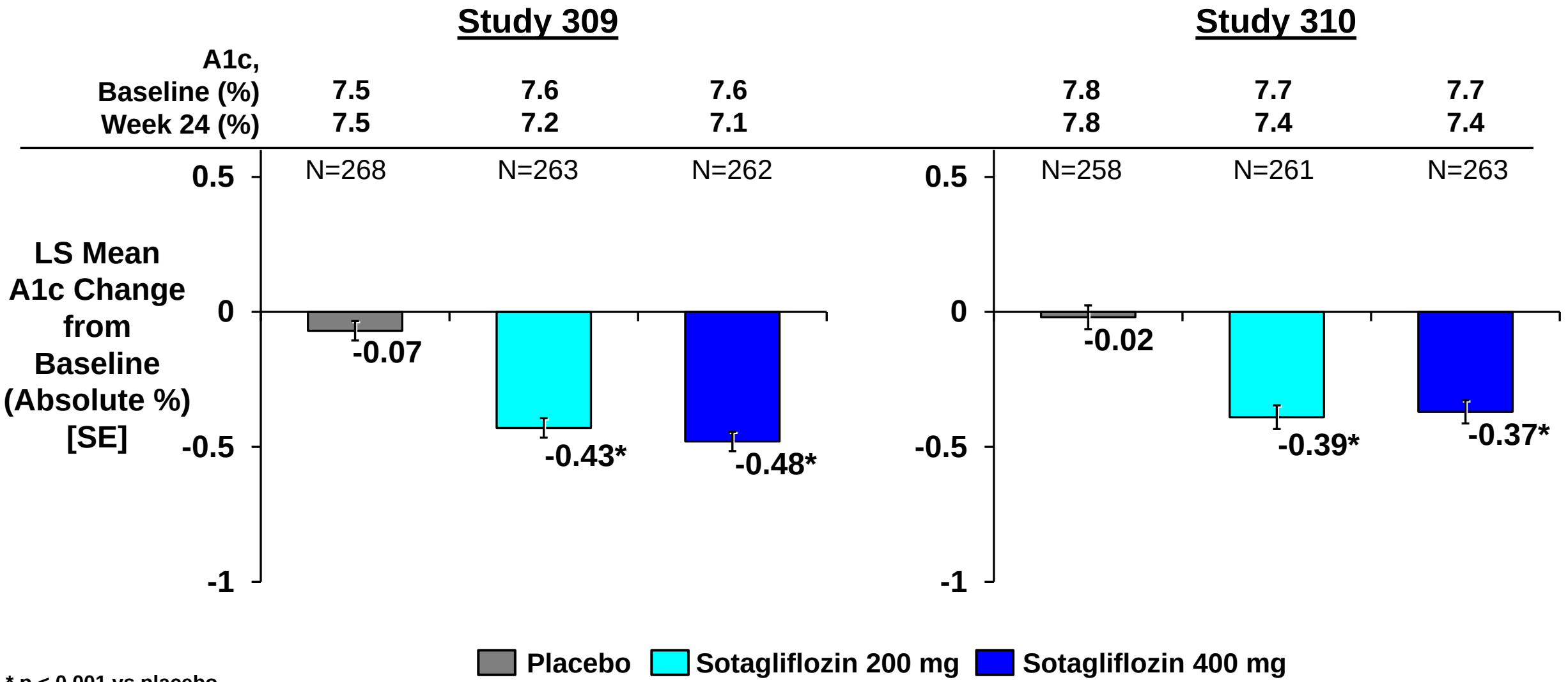
Studies 309 / 310: A1c Efficacy Observed Through Week 52 for Sotagliflozin Treated Patients



Studies 309 / 310: Sotagliflozin Reduced Total Insulin Dose at Week 24

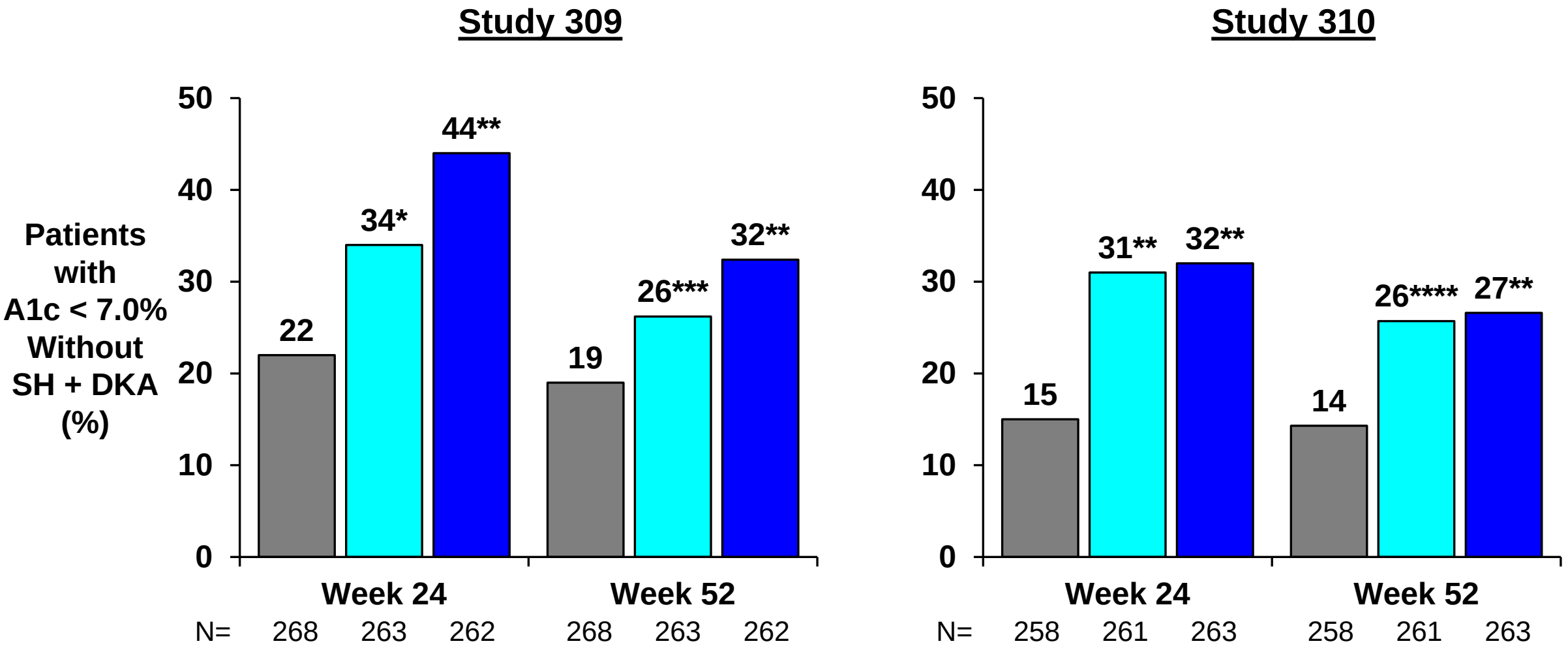


Studies 309 / 310: Sotagliflozin Produced Statistically Significant A1c Decrease vs Placebo at Week 24

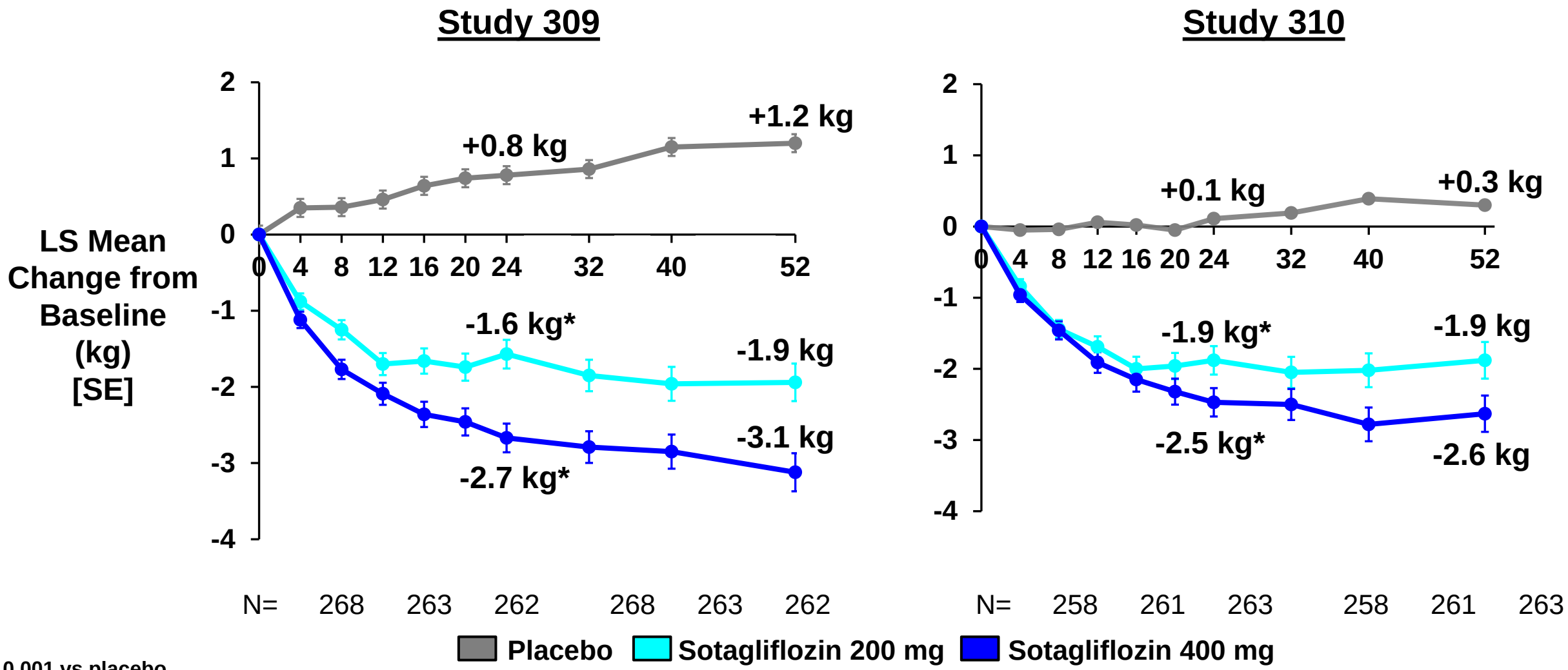


* p < 0.001 vs placebo

Studies 309 / 310: Sotagliflozin Provided Greater Net Benefit at Weeks 24 and 52

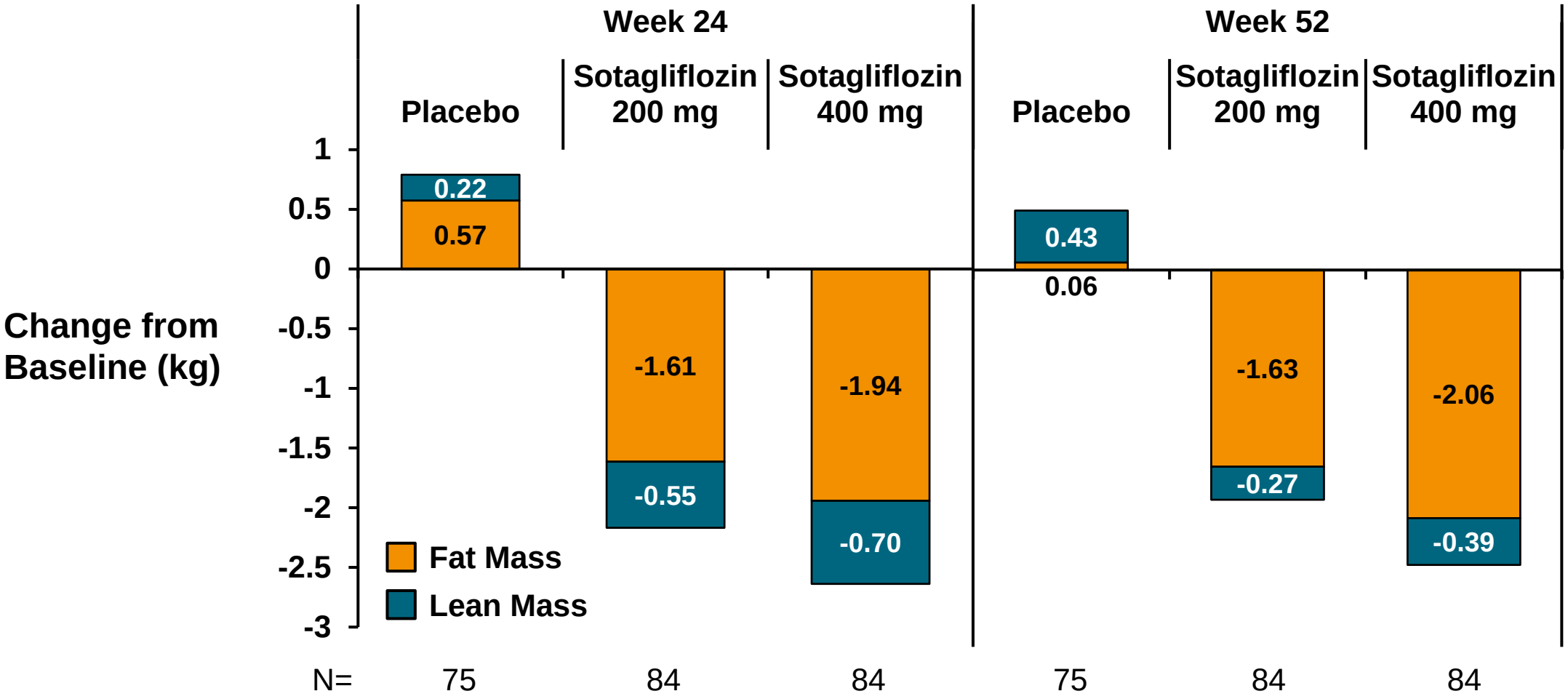


Studies 309 / 310: Sotagliflozin Significantly Reduced Body Weight at Weeks 24 and 52



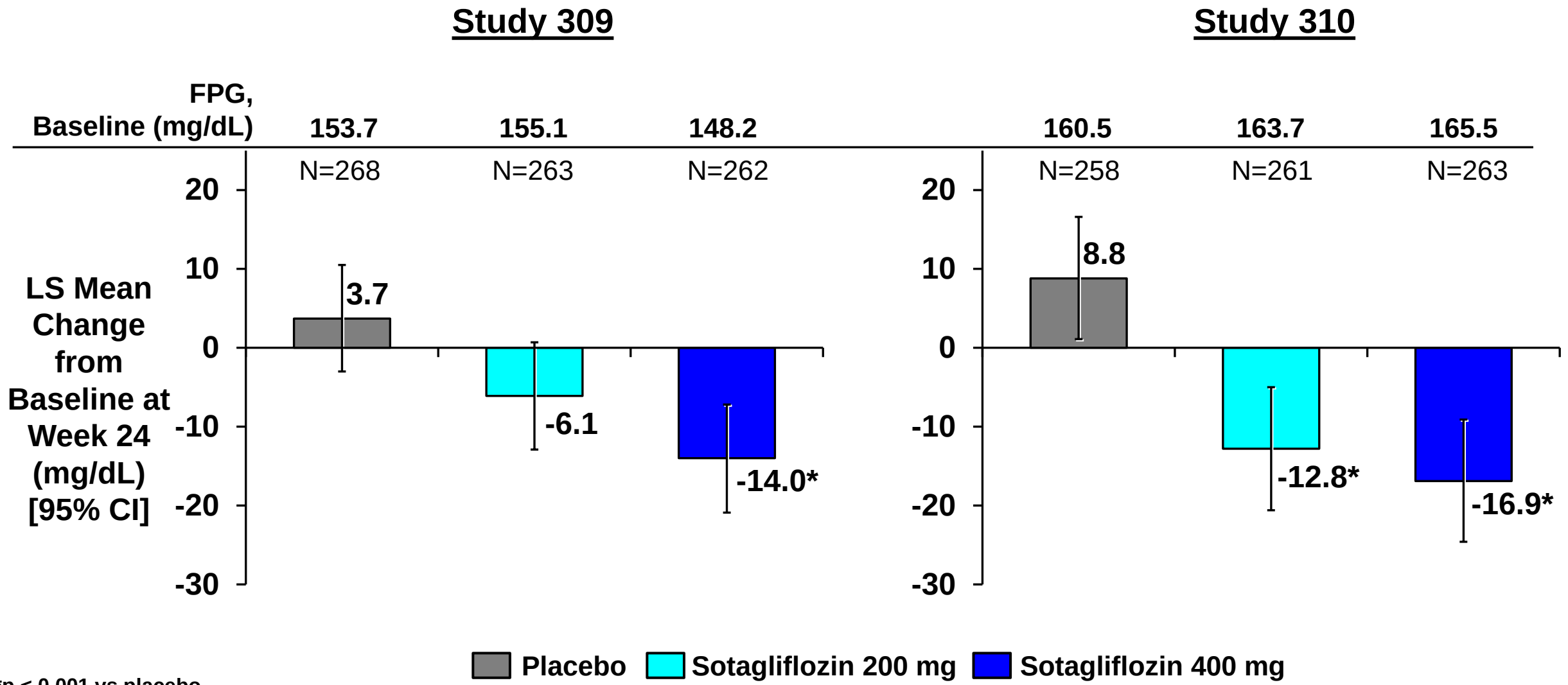
p < 0.001 vs placebo

Sotagliflozin Reduced Fat Mass vs Placebo



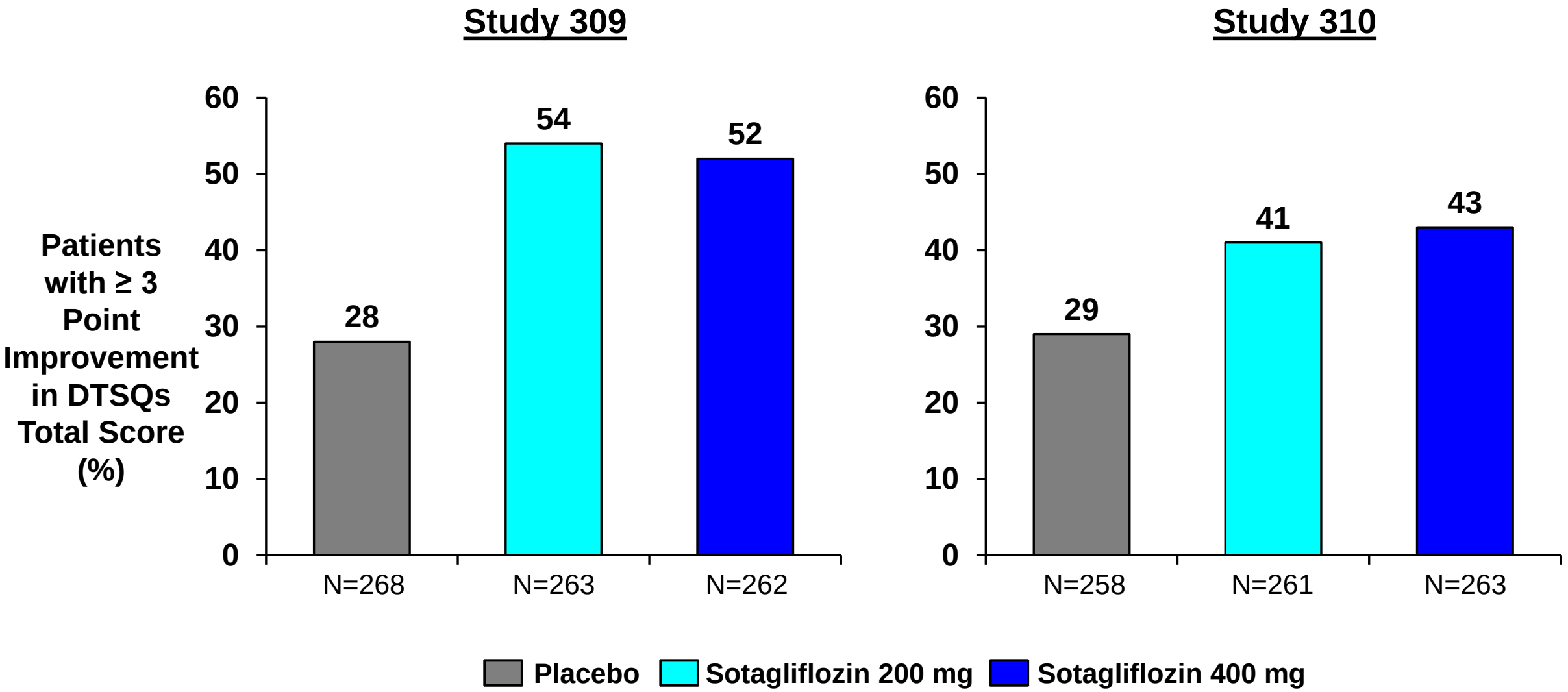
Results of body composition measured by DXA from Pooled Studies 309 / 310

Studies 309 / 310: Sotagliflozin Significantly Decreased FPG

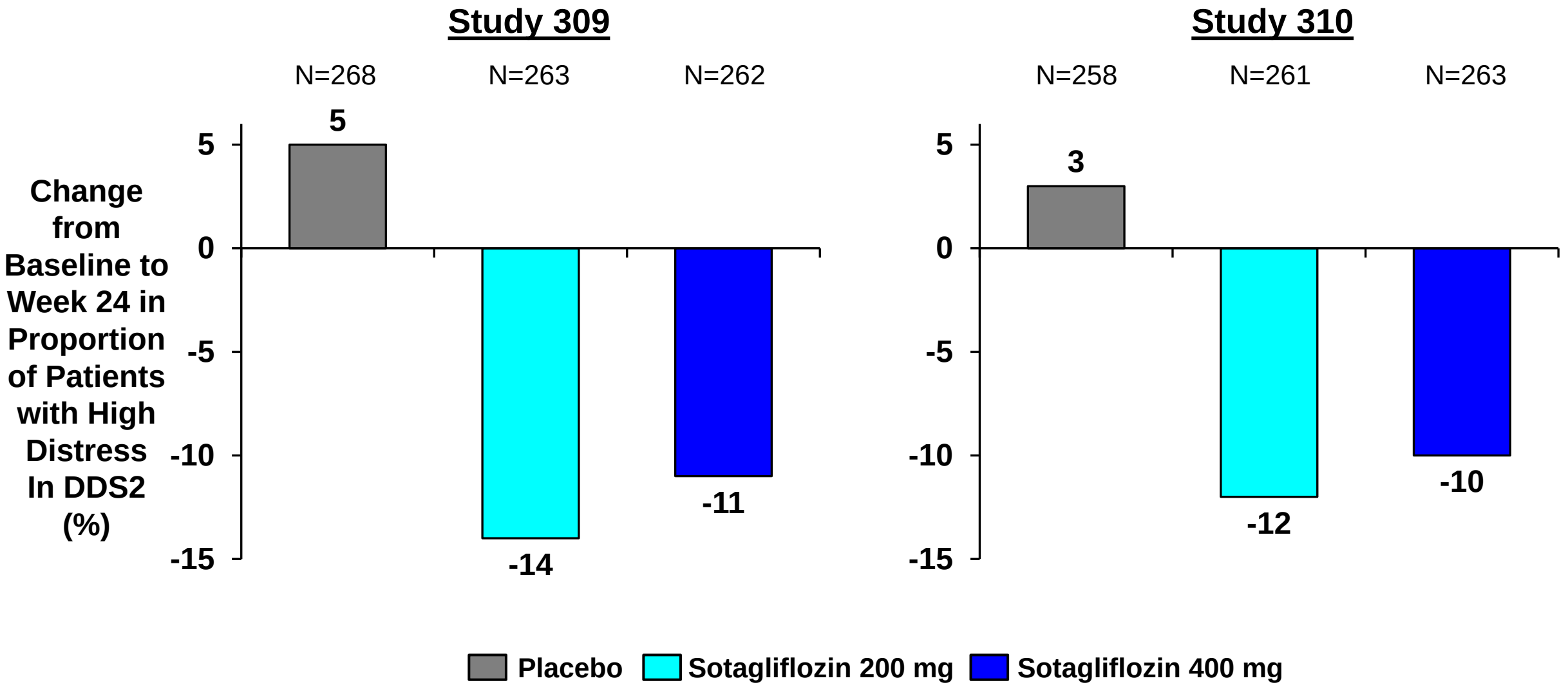


*p < 0.001 vs placebo

Studies 309 / 310: More Patients on Sotagliflozin Reported Improvement in Treatment Satisfaction



Studies 309 / 310: Sotagliflozin Reduced High Distress



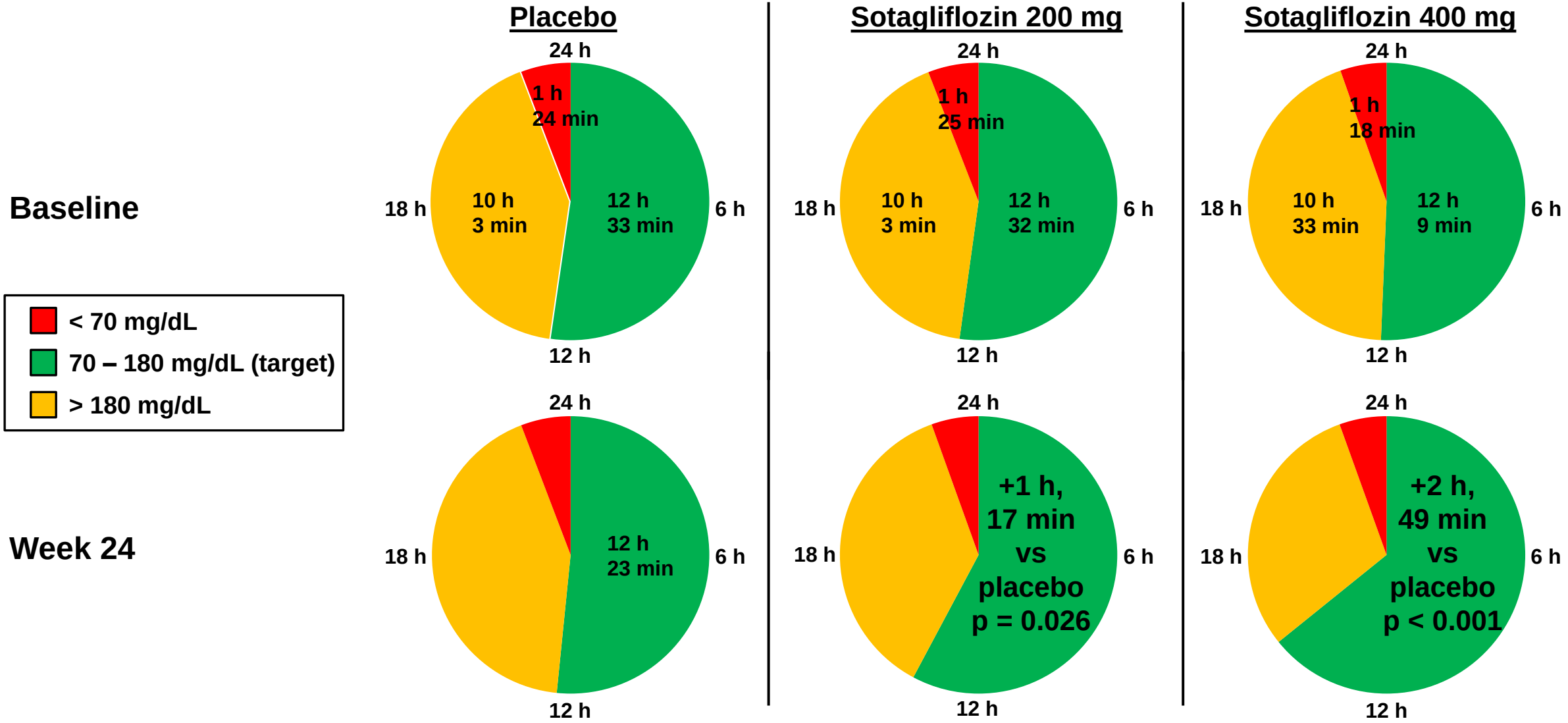
CGM Sub-Study

Pooled data from Studies 309 / 310

Pooled 309 / 310: CGM Sub-Study Design

- N = 278
  - n = 93 placebo
  - n = 89 sotagliflozin 200 mg
  - n = 96 sotagliflozin 400 mg
- Monitored with blinded-CGM device
  - Week -1 to Baseline, Week 3-4, Week 11-12, Week 23-24
- Assessment of PPG

Pooled 309 / 310: Sotagliflozin Increased Time in Range



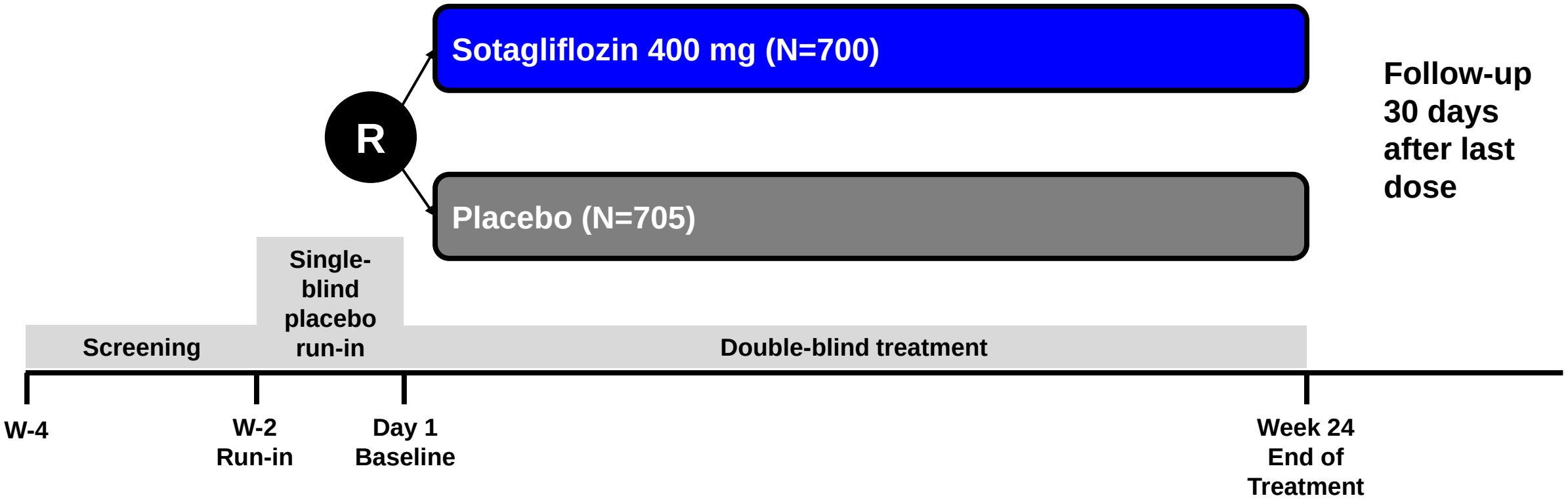
Pooled 309 / 310: Dose Response on Endpoints Beyond A1c

Improvements Beyond A1c	Parameter	Treatment Difference vs Placebo	
		200 mg	400 mg
Daily Glycemic Control	Time in range	+ 1h 17 m	+ 2h 49m
	FPG (mg/dL)	-15.7	-21.4
	PPG (mg/dL)	-34.8	-41.0
	Severe hypoglycemia (per 100 PY)*	-2.0	-3.4
Other Benefits	SBP (mmHg)	-2.0	-3.5
	Body weight (kg)	-2.2	-3.0

*Risk Reference of EAIR, 52 week data

Study 312: Design and Efficacy Results

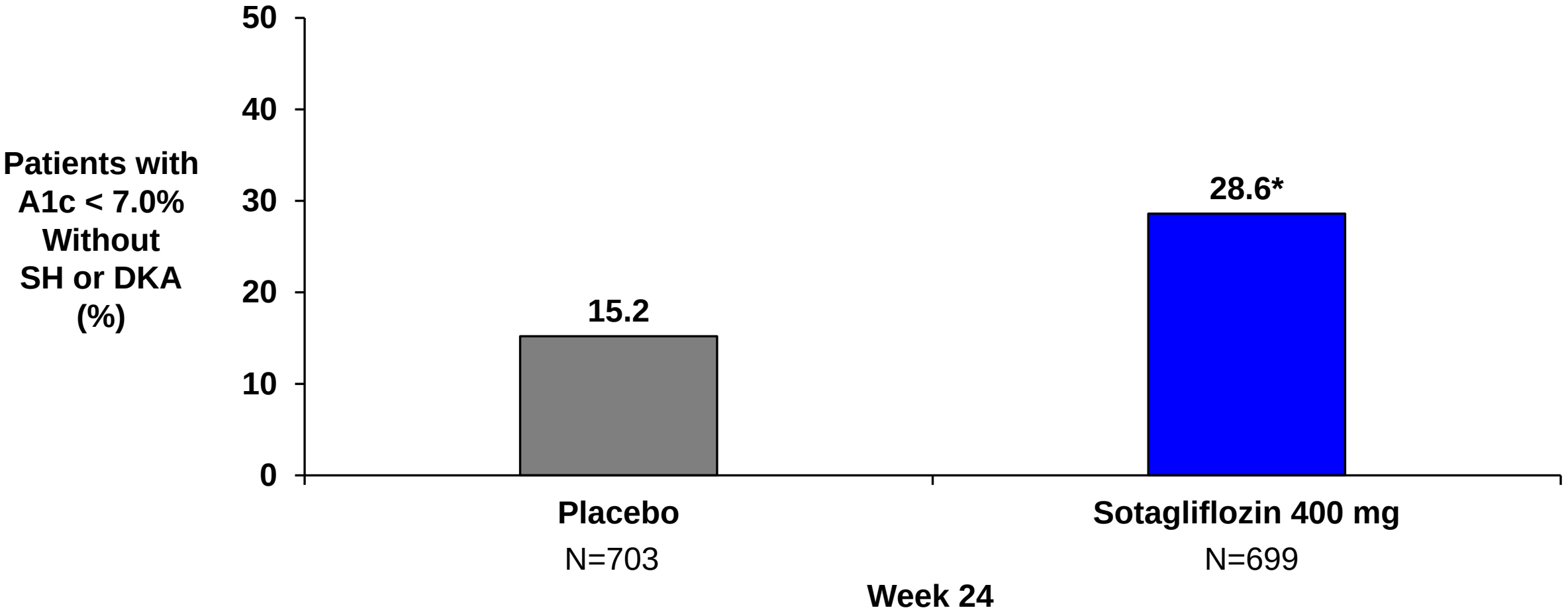
Study 312: Clinical Design



Primary endpoint: Net benefit

- Proportion of patients with A1c < 7.0% at Week 24 without SH or DKA

Study 312: Net Benefit Greater for Sotagliflozin 400 mg vs Placebo



* p < 0.001 vs placebo

Study 312: Secondary Endpoints Results

	Sotagliflozin 400 mg	
	Difference from Placebo	p-value
A1c change from Baseline at Week 24 (%)	-0.46	< 0.001
Body weight change from Baseline at Week 24 (kg)	-3.0	< 0.001
SBP change from Baseline (≥ 130 mmHg at Baseline) at Week 16 (mmHg)	-3.5	0.002
Bolus insulin change from Baseline at Week 24 (IU/day)	-2.84	< 0.001

Hypoglycemia

Positive Findings for Hypoglycemia with Sotagliflozin

- Safety endpoint
  - Examined on basis of MoA, rates, and incidences
- Key findings
  - More hypoglycemic events with blood glucose ≤ 55 mg/dL on placebo
  - More patients with investigator-reported and positively-adjudicated severe hypoglycemia on placebo

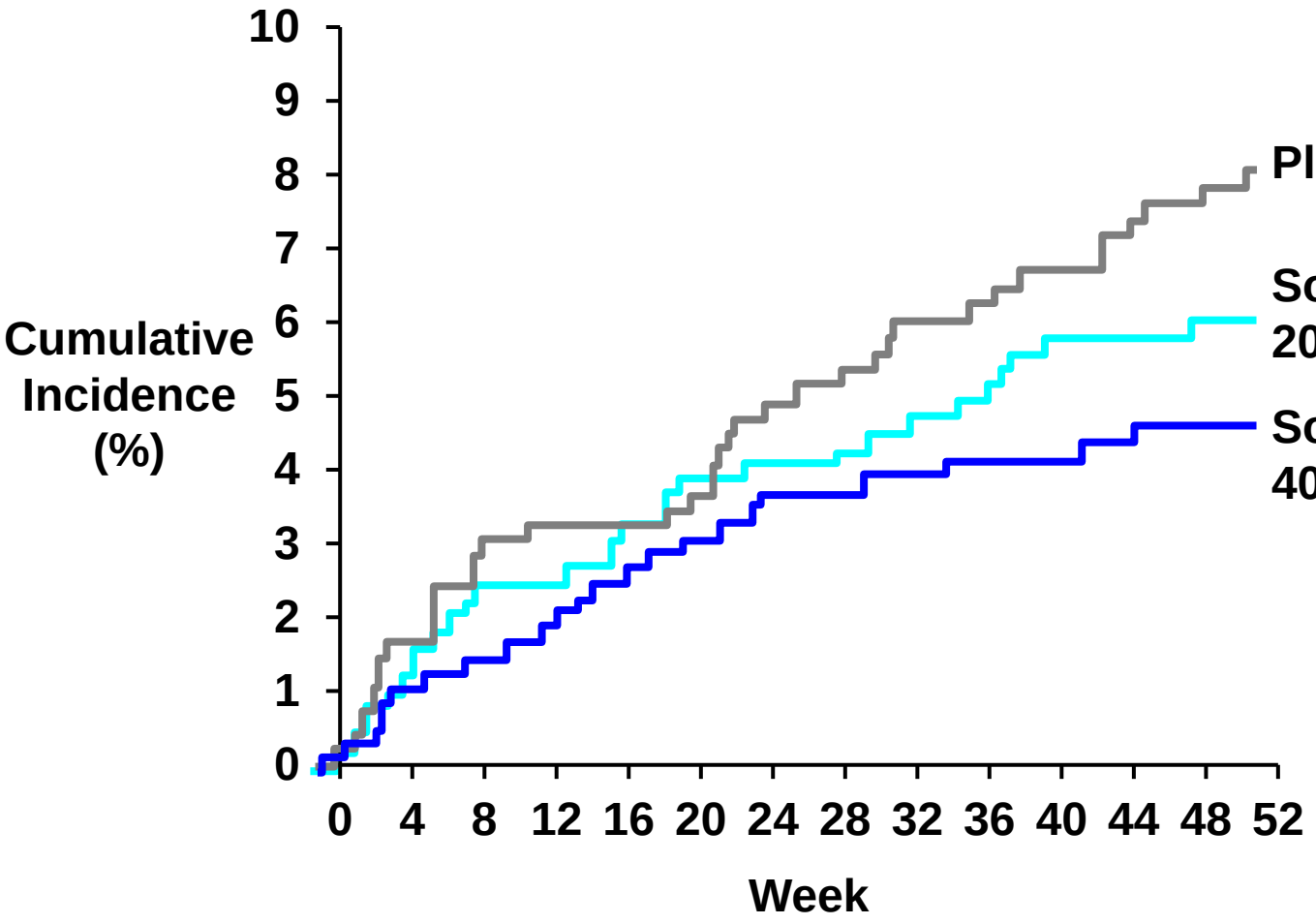
Evaluation of Hypoglycemia

- Hypoglycemia detected through SMBG measurements uploaded to central database
  - > 2 million values
  - Presence or absence of hypoglycemic symptoms noted on special collection form
- Severe hypoglycemia detected through reporting and independently adjudicated
  - Defined as requiring help from others, loss of consciousness, or seizure

More Documented Symptomatic Hypoglycemia Events (≤ 55 mg/dL) with Placebo

	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Pooled 309 / 310			
Number of events	6,551	5,190	5,115
Rate ratio (95% CI) Nominal p-value		0.78 (0.68, 0.88) p = 0.0001	0.80 (0.70, 0.91) p = 0.0006
Study 312			
Number of events	3,310		2,479
Rate ratio (95% CI) Nominal p-value			0.76 (0.68, 0.86) p < 0.0001

More Patients with Positively-Adjudicated Severe Hypoglycemia over 52 Weeks on Placebo



		Cox Model	FDA GLM*
Placebo	7.4%		
Sotagliflozin 200 mg	5.7%	HR 0.75 p=0.2434	p=0.2696
Sotagliflozin 400 mg	4.4%	HR 0.58 p=0.0377	p=0.0370

Pooled Studies 309 / 310

*FDA Briefing Book; GLM: generalized linear model

Sotagliflozin Added to Insulin Provided Improvement in Glycemic Control vs Insulin Alone

- Significant reductions in A1c vs placebo at Weeks 24 and 52
- Benefits beyond A1c reduction
  - PPG and time in range
  - Reductions in body weight and systolic blood pressure
  - Improvement in PROs
- Hypoglycemia data relevant
  - Glycemic control without higher symptomatic and severe hypoglycemia seen on insulin alone
  - Supports use of sotagliflozin

Clinical Safety Results

Klaus Henning Jensen, MD

Head of Diabetes, Cardiovascular and Metabolism Development

Sanofi

Safety Overview

- Sotagliflozin generally well-tolerated
- Class-related effects (genital mycotic infection, volume depletion) consistent with SGLT2 inhibitor class
- Increased risk of ketosis and DKA
  - Risk consistent with off-label SGLT2 inhibitor use
- DKA effectively managed through risk management plan
  - Learnings from clinical trial, off-label SGLT2 use, and expert clinical guidance

Safety Exposure

- Safety database included 30 clinical studies

	Patients Treated with Sotagliflozin	Sotagliflozin Exposure
	N	Patient Years
Phase 3 Studies 309 / 310 T1D (52 weeks)	1,049	957
Phase 2 / 3 Studies T1D	1,915	1,290
Phase 2 / 3 Studies T1D and T2D	2,175	1,343

Pooled 309 / 310: Overview of Adverse Events

Patients with AEs AE by MedDRA PT*	Placebo N=526 %	Sotagliflozin 200 mg N=524 %	Sotagliflozin 400 mg N=525 %
Any AE	71.1	75.0	74.3
Any AE leading to discontinuation	3.8	4.4	6.7
DKA	0	0.8	1.9
Diarrhea	0.4	0.4	0.6
Any SAE	7.0	10.1	9.5
DKA	0.6	3.6	5.0
Hypoglycemia	1.0	1.0	1.0
Deaths (all Phase 2 / 3 studies)	3 (0.2)	0	1 (0.08)

* DKA, diarrhea, hypoglycemia shown here are investigator-reported events

Events of Special Interest (EOSI) Evaluated in Sotagliflozin T1D Program

- Documented and Severe Hypoglycemia*
- DKA*
- Major Adverse Cardiovascular Events (MACE)*
- Drug induced liver injury (DILI)*
- Genital mycotic infection
- Volume depletion
- UTI
- Amputation
- Renal events
- Bone fracture
- Diarrhea
- Malignancy

*** Events Adjudicated by Clinical Events Committees (CECs)**

Changes in Early Clinical Features of DKA with SGLT2 Inhibitors

Early symptoms and signs

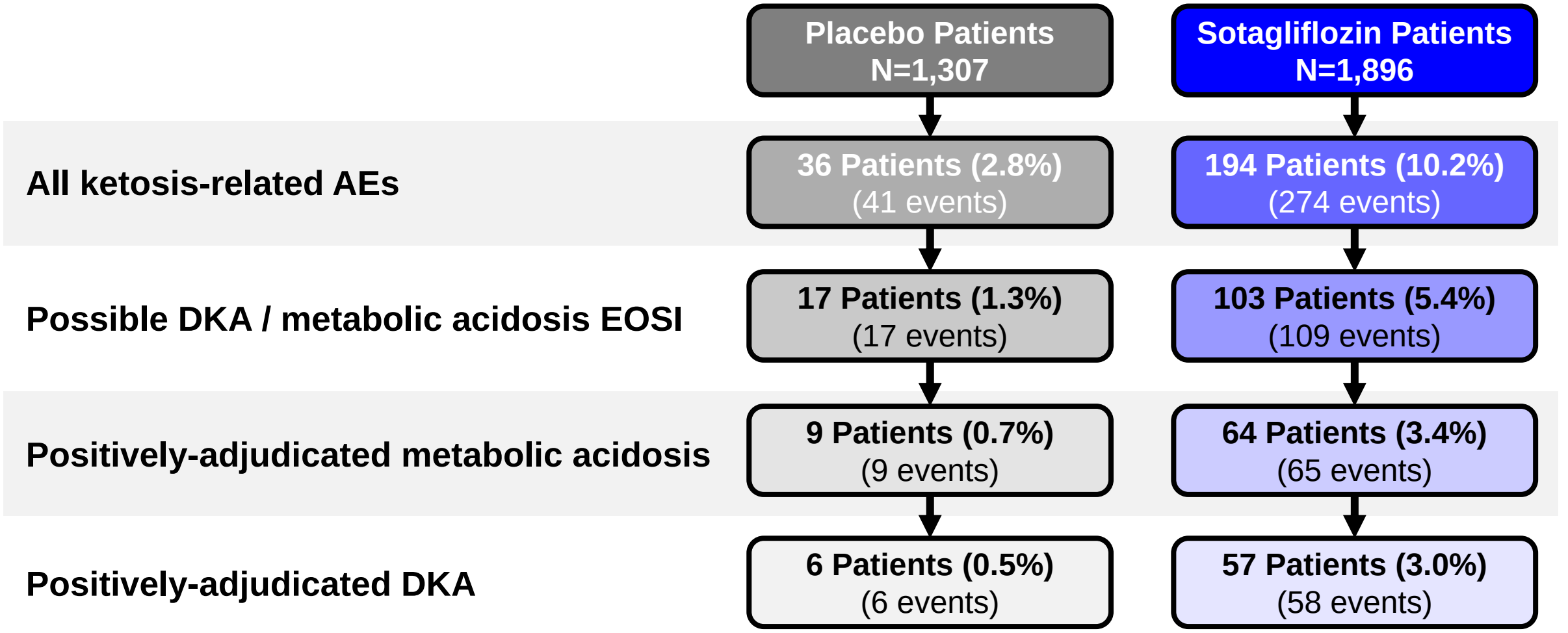
- High blood glucose levels
- Increased urination
- Increased thirst
- High ketone levels

Later ketosis-related symptoms and signs

- Weakness, sleepiness
- Dry, flushed skin
- Nausea, vomiting, abdominal pain
- Difficulty breathing, fruity breath

ADA. What to know about diabetic ketoacidosis. www.diabetes.org.dka; Kitabchi *et al*. *Diabetes Care* 2009

Phase 2 / 3 T1D Studies: CEC Assessment of Potential DKA Events



All Phase 2 / 3 T1D Studies: Incidence of Positively-Adjudicated DKA

	Placebo N=1,307	All Sotagliflozin N=1,896
Frequency of patients with DKA	6 (0.5%)	57 (3.0%)
EAIR for DKA, per 100 PY	0.7 (0, 1.4)	4.1 (3.0, 5.2)
Relative Risk of the EAIR, vs placebo (95% CI)	-	6.6 (3.0, 17.1)
Risk Difference of EAIR, minus placebo (95% CI)	-	3.6 (2.5, 4.8)

EAIR: Exposure Adjusted Incidence Rate
Rates, ratios, and risk differences calculated using stratification to take into account differences in protocol design across phase 2 / 3 studies

Pooled 309 / 310: Numerical Increase in DKA Risk

	Placebo N=526	Sotagliflozin 200 mg N=524	Sotagliflozin 400 mg N=525
Frequency of patients with DKA	1 (0.2%)	15 (2.9%)	20 (3.8%)
EAIR for DKA, per 100 PY	0.2 (0. 0.6)	3.1 (1.5, 4.7)	4.2 (2.4, 6.0)
Relative Risk of the EAIR, vs placebo (95% CI)	-	14.8 (2.7, 315.0)	19.9 (3.7, 416.3)
Risk Difference of EAIR, minus placebo (95% CI)		2.9 (1.3, 4.5)	4.0 (2.1, 5.9)

Phase 2 / 3 T1D Studies: DKA Characterization

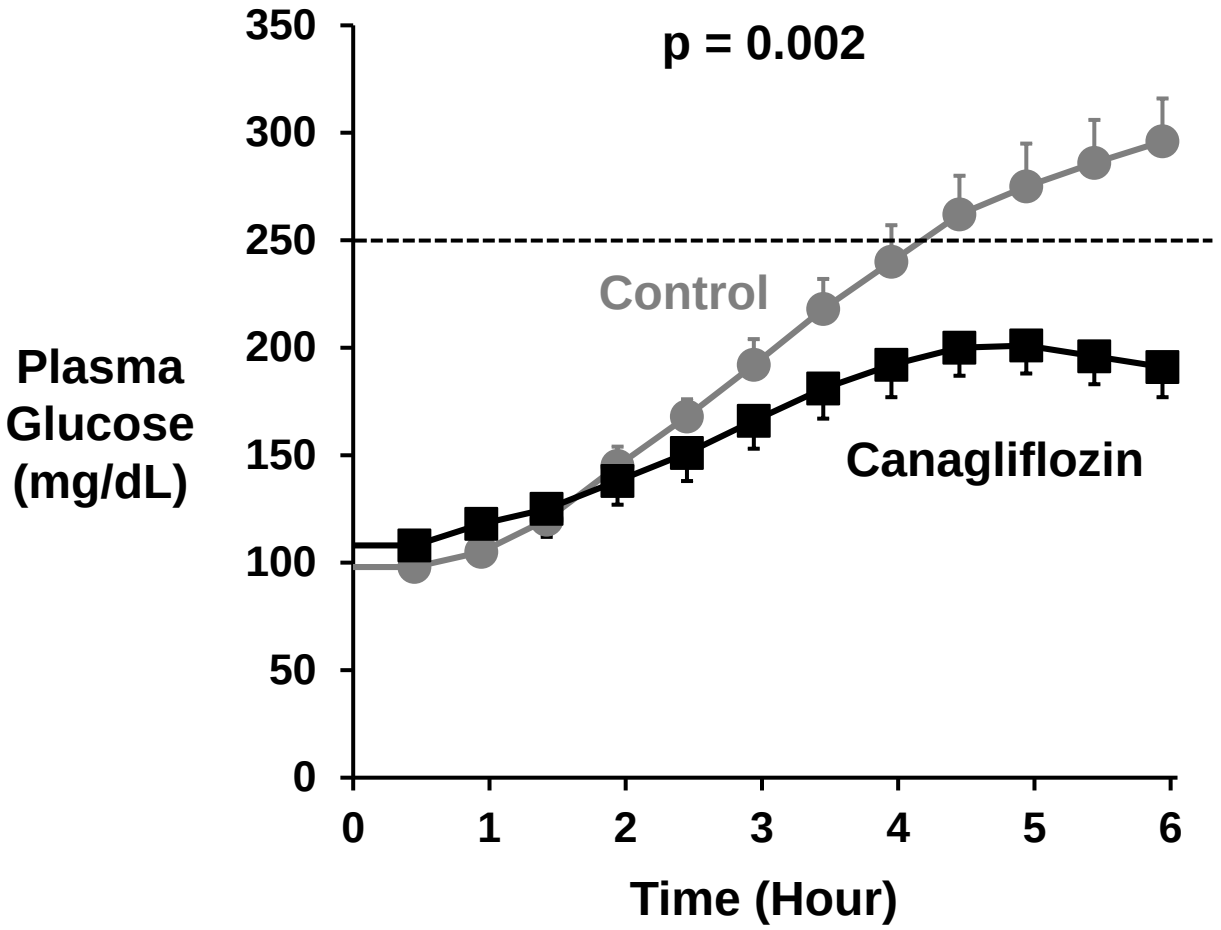
DKA Events	Placebo N=6	All Sotagliflozin N=58
Classified as SAE	5 (83%)	56 (97%)
Fatal	0	0
Hospitalizations	5 (83%)	54 (93%)
Mean DKA duration, days	5.5	4.8
Event severity*		
Mild	3 (50%)	8 (14%)
Moderate	3 (50%)	30 (52%)
Severe	0	20 (34%)
AEs leading to discontinuation	1 (17%)	23 (40%)

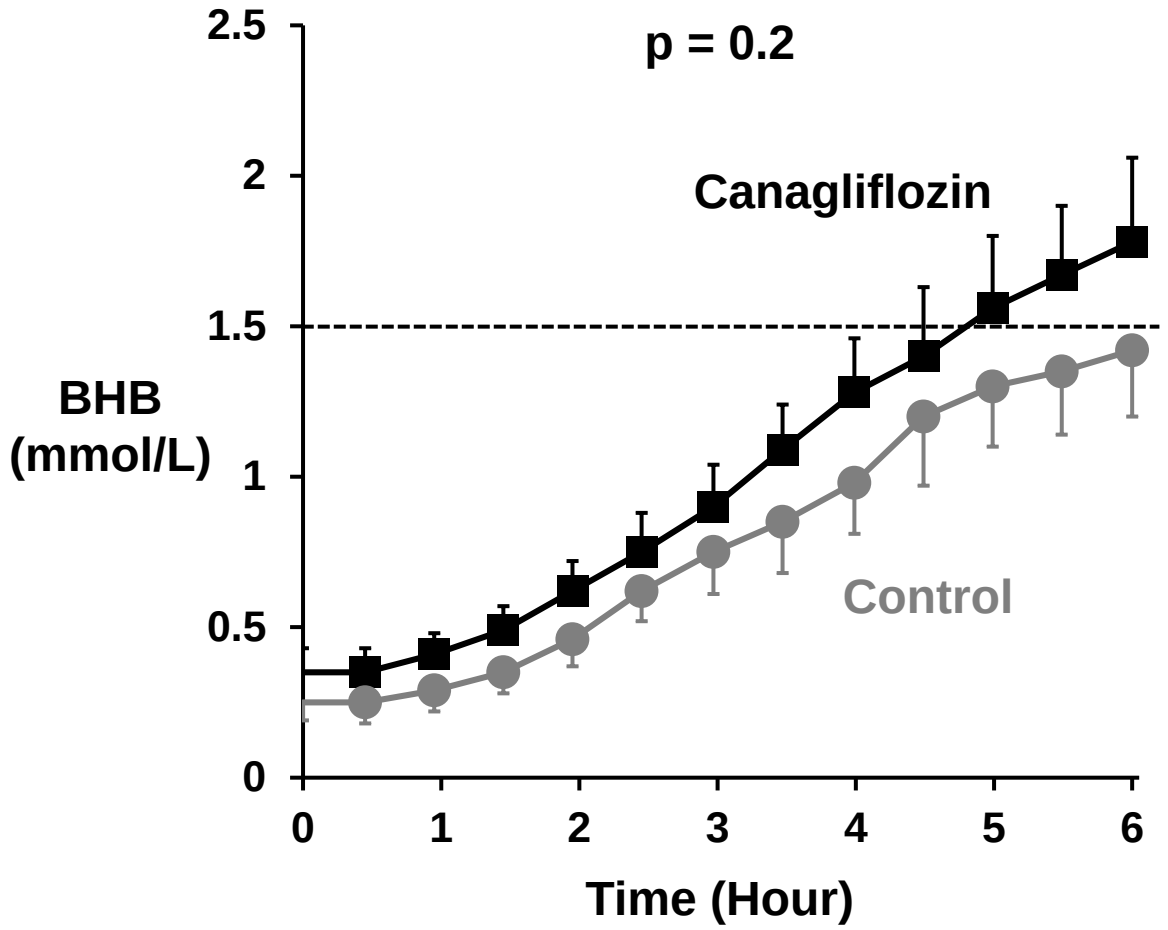
* Presented severity data using modified ADA Consensus severity criteria (without glucose criterion > 250 mg/dl), rather than investigator-reported severity

Pooled 309 / 310: No Events of DKA in Patients with BG < 150 mg/dL

	Placebo N=1	Sotagliflozin 200 mg N=16	Sotagliflozin 400 mg N=20
> 250 mg/dL (> 13.9 mmol/L)	1 (100%)	8 (50%)	15 (75%)
150 to 250 mg/dL (8.3 to 13.9 mmol/L)	0	8 (50%)	5 (25%)
< 150 mg/dL (< 8.3 mmol/L)	0	0	0

Plasma Glucose and BHB Levels During Control and Canagliflozin Treatment Studies





Recreated from Figure 1 from Patel et al., Diabetes Technology & Therapeutics, 2017

Phase 2 / 3 T1D Studies: DKA Triggers Inform Risk Management Strategy

DKA Triggers	Placebo N=6	All Sotagliflozin N=58
Acute infection or illness	2 (33%)	26 (45%)
Insulin reduction or interruption		
Insulin reduction / missed dose	1 (17%)	9 (16%)
Pump interruption	1 (17%)	18 (31%)
Other		
Alcohol	2 (33%)	3 (5%)
Low carb diet	0	1 (2%)
Excess exercise	0	1 (2%)
No identified triggers	1 (17%)	5 (9%)

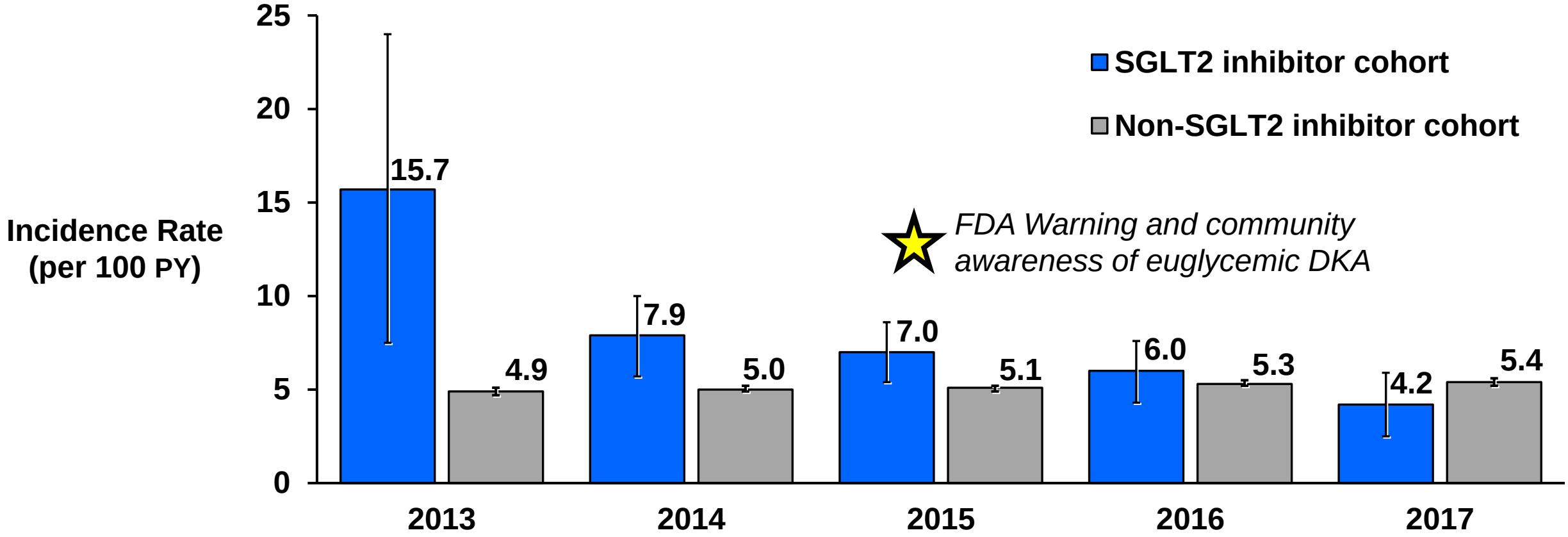
Evaluation of Potential DKA Risk Factors

- Analyses performed to evaluate potential DKA risk factors
  - Baseline patient characteristics
  - Relationship between insulin dose and DKA
- No subgroup identified with substantial increase in DKA risk above general trial population
- Several factors independent of sotagliflozin, identified with modest association to DKA risk
  - Higher risk: Prior DKA history, insulin pump use, and female
  - Lower risk: Higher insulin doses or no insulin dose reduction
- Findings used to inform DKA risk management strategy

Postmarketing DKA Reports with SGLT2 Inhibitors (MarketScan Database)

- Experience from off-label use of available SGLT2 inhibitors
- Evaluation of incidence rates of hospitalization for DKA
- MarketScan: large US-based healthcare claims database
- Incidence rates for DKA in patients with T1D using SGLT2 inhibitors vs patients not on these drugs

Hospitalized DKA in Adult T1D Patients Stratified by Use of SGLT2 Inhibitors (MarketScan Database, 2013-2017)



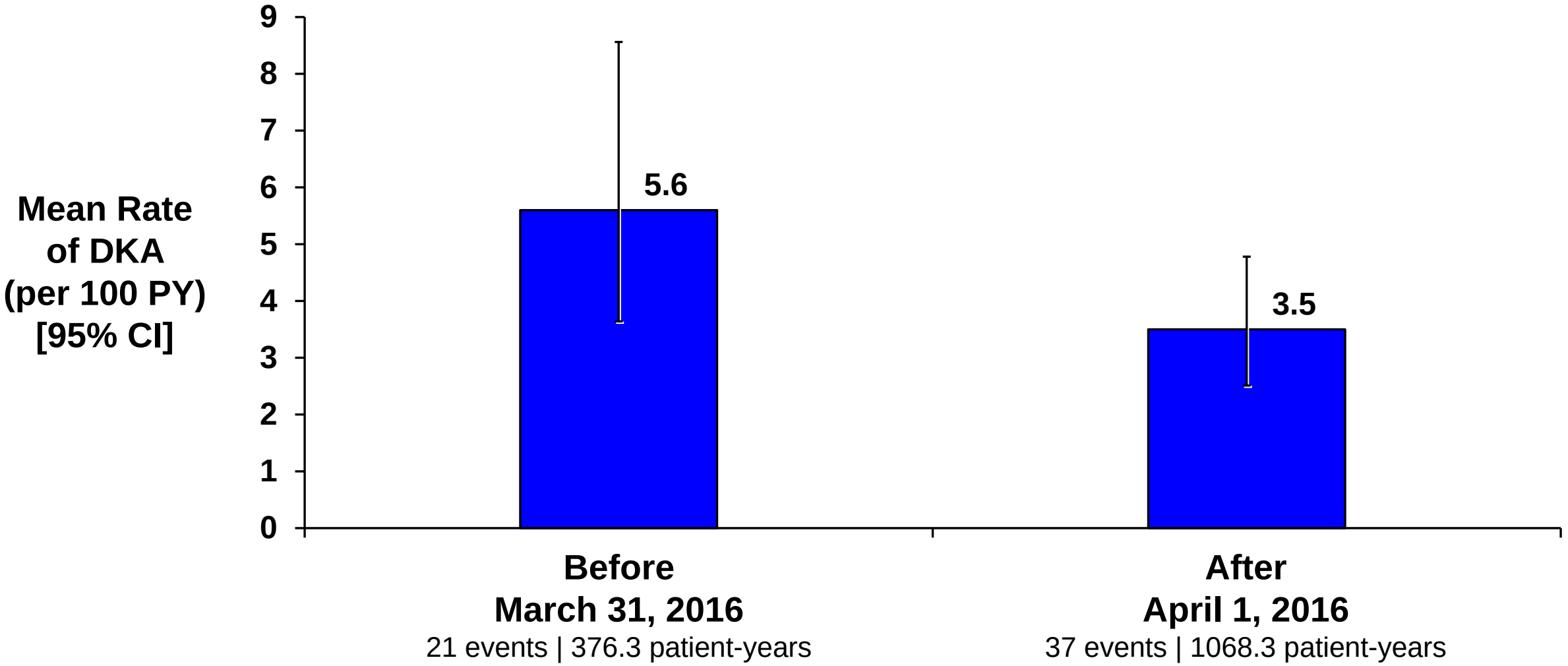
Number of patients at risk

	2013	2014	2015	2016	2017
SGLT2 inhibitor cohort	411	2,049	2,341	1,842	1,327
Non-SGLT2 inhibitor cohort	124,742	117,262	89,062	85,283	73,682

Measures Taken in Clinical Program to Minimize DKA Risk

- Initial steps
  - Exclusion of patients with recent DKA or elevated screening BHB
- Following FDA DKA warnings (2015)
  - Communication about Euglycemic DKA risk with SGLT2 inhibitors
  - Additional education for patients and investigators
    - Signs and symptoms for ketosis / DKA
    - Circumstances which may increase risk (surgery, infection, etc)
    - Guidance on early intervention and avoidance of progression
  - Provision of urine ketone sticks and blood BHB meters

Effect of Enhanced Risk Mitigation on DKA Rate in Clinical Trials (2015-2017)



Risk Management Strategy

Patient Selection

Ketone Monitoring

Adequate Insulin Dosing

Broad Risk Communication

Appropriate Patient Selection

- Disease not controlled on SOC (intensive insulin therapy)
- Engaged patients capable of day-to-day management of T1D
  - Adept at managing insulin dose adjustments
  - Recognize at-risk situations and apply sick-day rules
  - Willingness to monitor ketones essential
- Do not start sotagliflozin
  - Recent or recurrent DKA
  - Ketosis at baseline
  - Risk for ketosis (e.g. excessive alcohol use, ketogenic diets)

Ketone Monitoring and Management

- Check ketones before and after starting treatment
- Insulin pump patients check ketones 3-4 hours after infusion set or component changes
- Stop sotagliflozin and seek medical attention
  - Mildly elevated ketones with clinical symptoms of ketosis / DKA
  - Moderately elevated ketones regardless of symptoms
- Consider restarting sotagliflozin
  - Complete event resolution
  - Correction of precipitating factors

Maintenance of Adequate Insulin Dosing

- Optimize insulin prior to starting therapy
- Cautious insulin reductions after starting sotagliflozin to avoid ketosis / DKA
- Consider discontinuing sotagliflozin if adequate insulin dosing cannot be achieved

Risk Communication Plan Targeting Both Healthcare Providers and Patients

Healthcare Providers

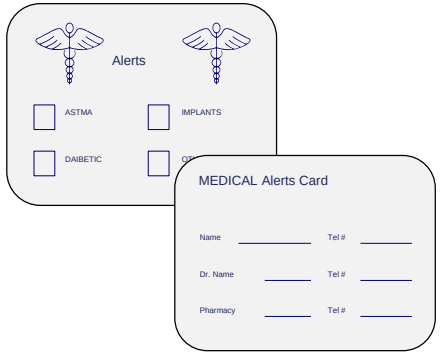
Product Labeling

- Core of DKA risk communication

HCP Communication Letter

- Sent within 60 days of approval
- DKA identification and management
- Target 1 million HCPs

Patients



Patient Alert Card

- In product carton
- Signs / symptoms, triggers, and management
- Portable - shown to HCPs in acute care setting

Medication Guide and Website

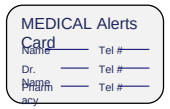
- Distributed with each prescription fill
- Complete information on product safety and DKA

Broad Risk Communication to Further Enhance DKA Messaging

Healthcare Providers

- Scientific programs to discuss T1D and DKA management
- Educational materials delivered to HCPs
- Publications
- National Congress Meetings
- Promotional speaker programs

Patients



- Patient Alert Card
- Education and messaging at point of care
- Patient tip sheet
- Patient education video
- Nurse outreach via the PSP
- Welcome email communication
- PSP SMS messaging

Post-Marketing Assessments to Evaluate Effectiveness of DKA Risk Mitigation

- Post-Authorization Safety Study (PASS)
  - Further monitor DKA risk in real-world setting
  - Compare risk of DKA with sotagliflozin to insulin alone
- Drug utilization study
  - Evaluate prevention, diagnosis, and treatment of DKA in patients treated with sotagliflozin
- Prescriber survey to assess effectiveness of risk communication

Sotagliflozin Safety Supports Use as Adjunct to Insulin in Patients with T1D

- Well-tolerated
- Safety profile largely consistent with SGLT2 class
- Less hypoglycemia vs insulin alone
- Increased risk of DKA
  - 3-4 excess cases per 100 PY
  - Well-characterized and consistent with class
  - Anticipated based upon MoA
  - Predictable with recognized triggers amenable to enhanced “for cause” ketone monitoring to prevent progression

Risk Management Plan Developed to Effectively Mitigate DKA Risk

- Feasibility suggested by SGLT2 inhibitor experience
  - Incidence rates comparable to standard of care therapy
- Plan focused on appropriate patient selection, targeted ketone monitoring, and maintenance of adequate insulin dosing
  - Supported through broad communication plan targeting key medical and patient stakeholders

Clinical Perspective

Juan Pablo Frias, MD

Medical Director and Principal Investigator
National Research Institute

Majority of Adults with T1D Not Achieving Glycemic Goals

- Challenges of insulin therapy
  - Weight gain, excessive glycemic variability, and hypoglycemia
- Hypoglycemia a leading cause of diabetes-related death in patients with T1D
- Patients and HCPs need adjunctive therapeutic agents
- Sotagliflozin meets needs in appropriate patients with T1D

Appropriate Patients for Sotagliflozin

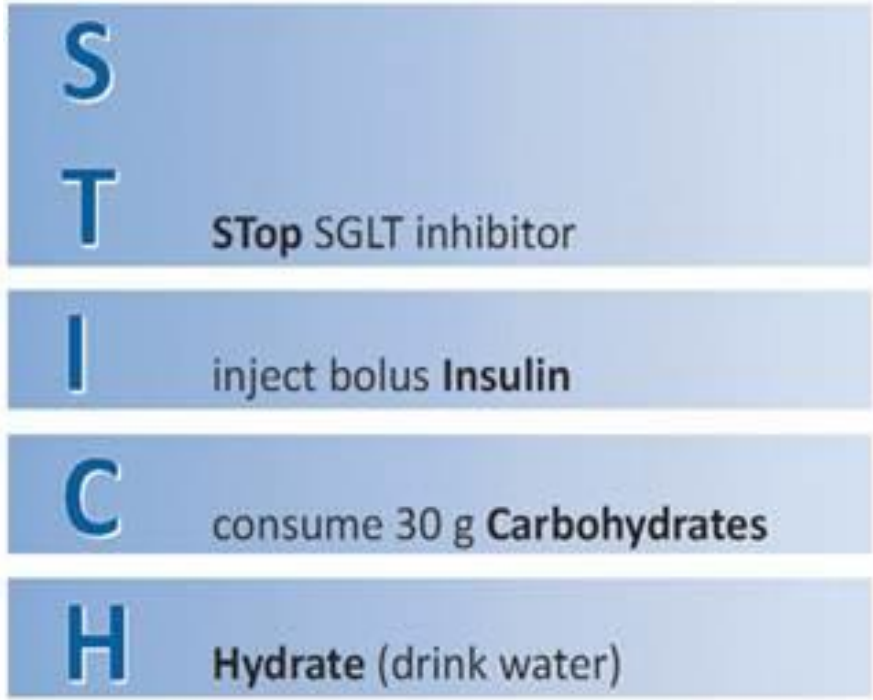
- Not achieving glycemic targets with insulin alone
- Significant glycemic variability
- Frequent hypoglycemia
- Because of known risk of DKA
  - Engaged patients
  - Willingness and ability to optimize insulin
  - Monitor ketones
  - Communicate to HCP

Patients NOT Appropriate for Sotagliflozin

- Not achieved best possible results with insulin alone
- Recurrent or unexplained DKA
- Ketogenic diet
- Not demonstrated ability to self-manage disease
- Difficulties complying with treatment plan

How I Will Use Sotagliflozin in Practice

- Instruct patients on risks and how to prevent, recognize, self-treat, and when to contact clinic
- Prevention and treatment of DKA in T1D ongoing practice
- STICH Protocol[1]
  - Treatment and prevention of DKA in patients using SGLT inhibitors



1. Garg, 2018

Proposed Safety Plan Will Mitigate DKA Risk

- Proposed steps commonplace in clinical care
  - Appropriate selection, patient education, and monitoring
- Sponsor's plan will further educate patients and HCPs and help reduce DKA
- MarketScan claims data reassuring that awareness and education over time will reduce incidence of DKA

Positive Benefit / Risk Ratio of Sotagliflozin

- Addresses unmet need in patients with T1D
- Reductions in A1c, body weight, and systolic blood pressure
- Improvement in time in range
- Patients more satisfied and less distressed than insulin alone
- Sotagliflozin much needed tool for HCPs

Sotagliflozin as an Adjunct to Insulin for Type 1 Diabetes

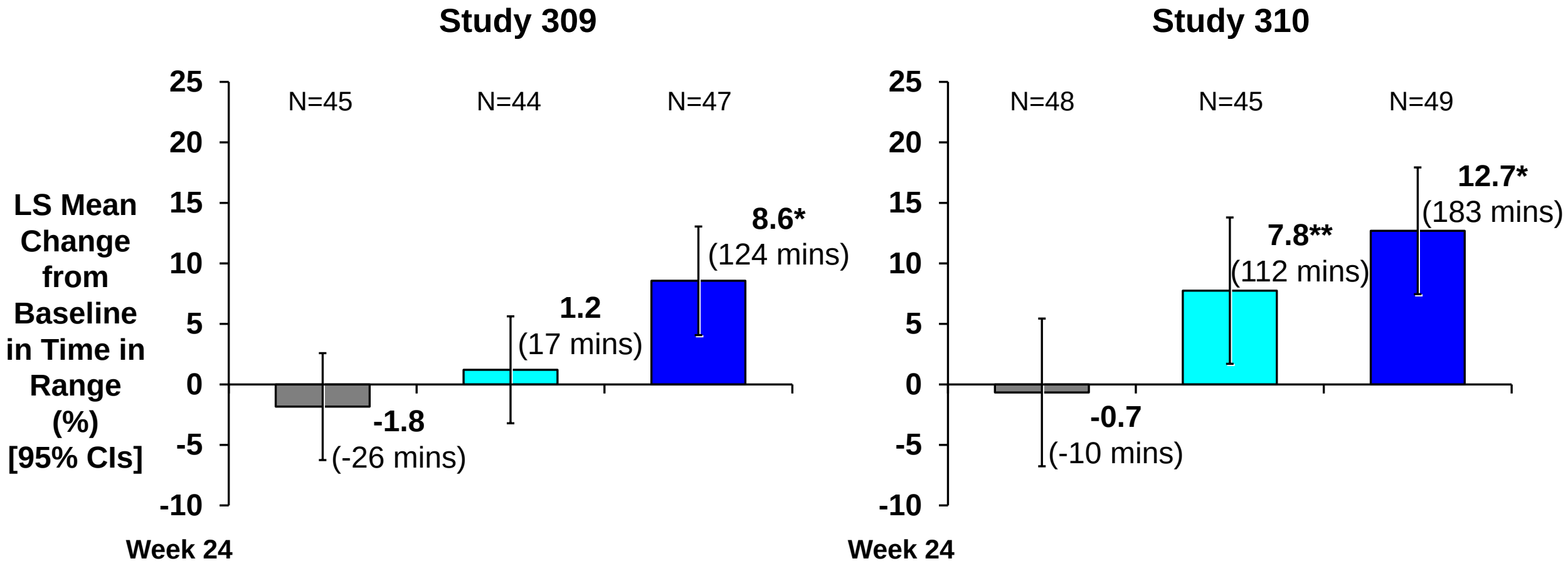
January 17, 2019

Sanofi / Lexicon Pharmaceuticals

Endocrinologic and Metabolic Drugs Advisory Committee

BACK-UP SLIDES SHOWN

Study 309 / 310: Time in Range (70 - 180 mg/dL)



* Nominal p-value < 0.001
** Nominal p-value = 0.044

Placebo | Sotagliflozin 200 mg | Sotagliflozin 400 mg

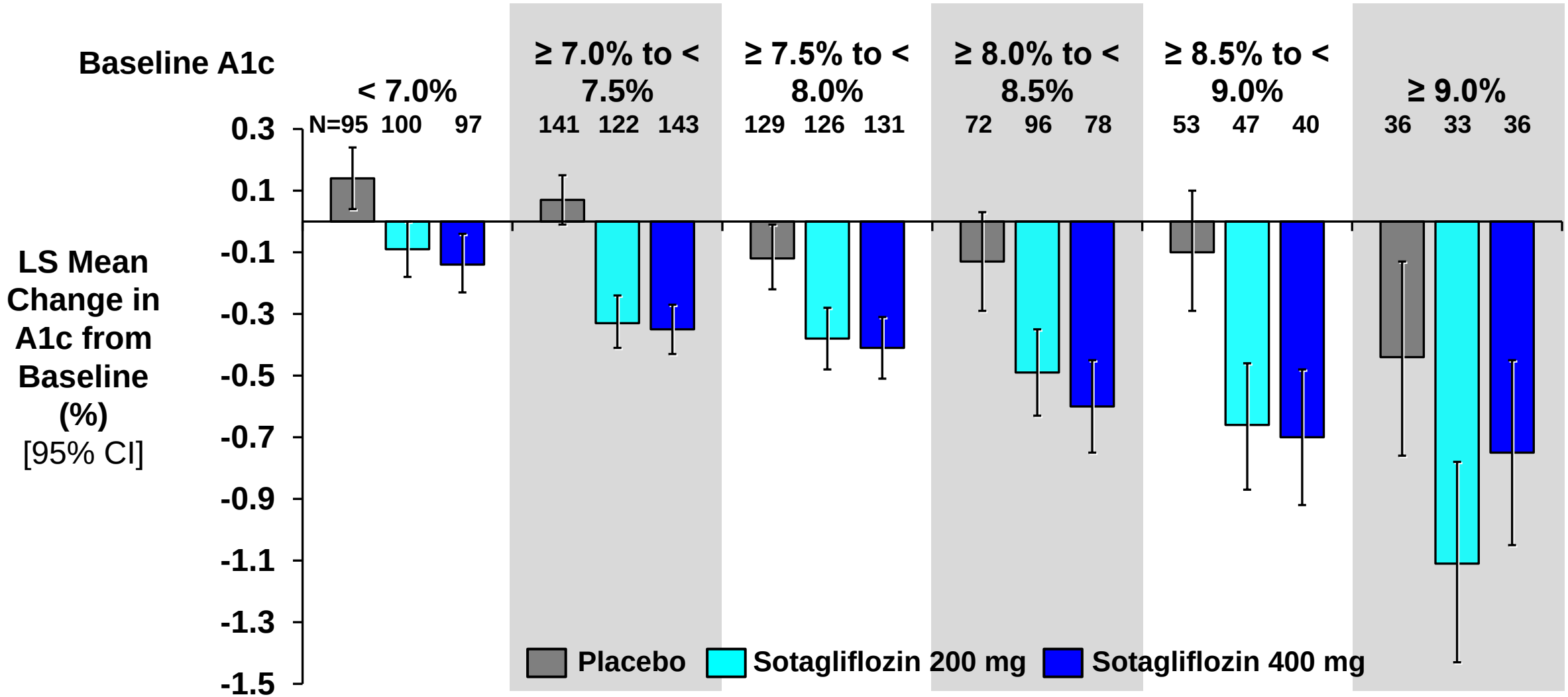
2-Item Diabetes Distress Screening Scale (DDS2)

Listed below are 2 potential problem areas that people with diabetes may experience.

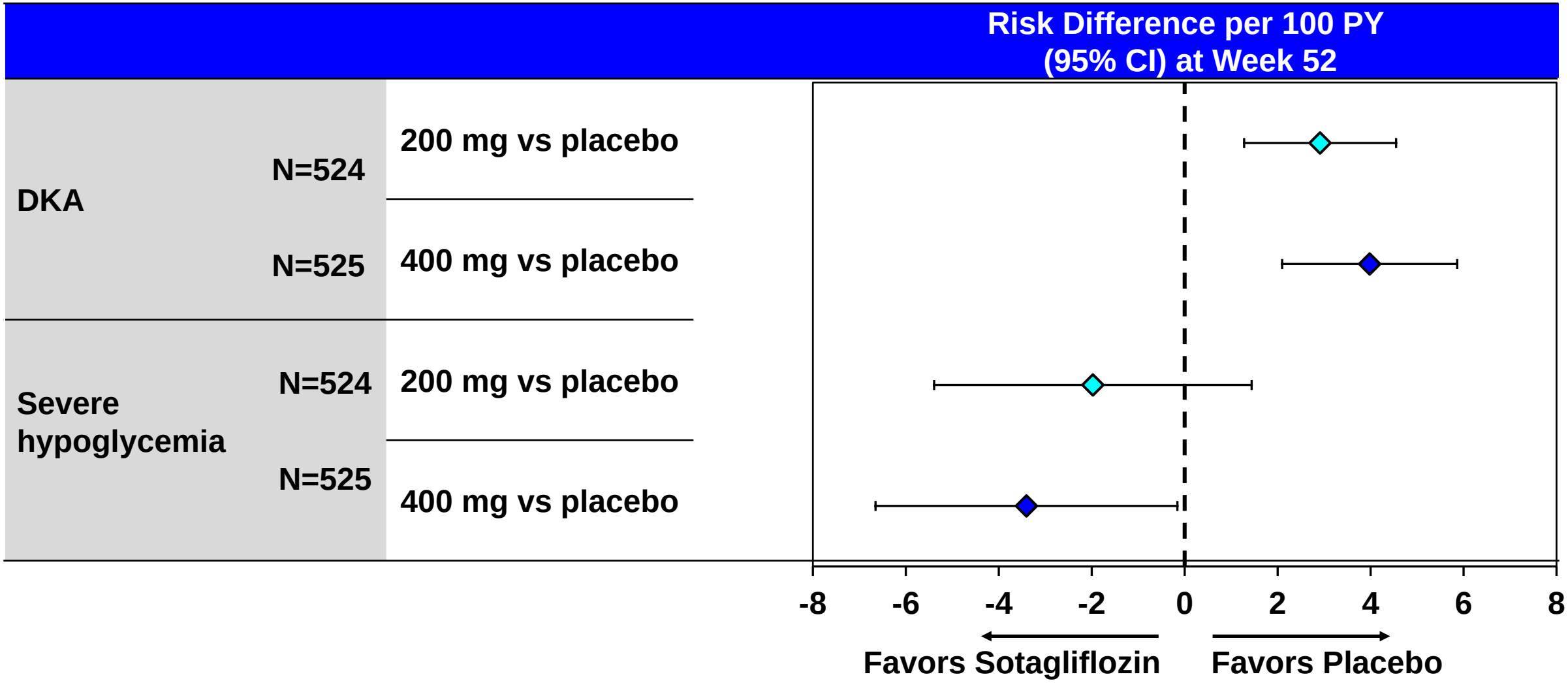
Each of the 2 items may have distressed or bothered you DURING THE PAST MONTH and circle the appropriate number.

	Not a problem	A Slight Problem	A Moderate Problem	Somewhat Serious Problem	A Serious Problem	A Very Serious Problem
1. Feeling overwhelmed by the demands of living with diabetes.	1	2	3	4	5	6
2. Feeling that I am often failing with my diabetes routine.	1	2	3	4	5	6

Pooled 309 / 310: A1c Reduction (%) at Week 24 by Baseline A1c



Risk Difference of DKA and Severe Hypoglycemia



Pooled 309 / 310: Sotagliflozin 200 mg and 400 mg Dose Comparison

Improvements Beyond A1c	Parameter	Treatment Difference vs Placebo	
		200 mg	400 mg
Daily Glycemic Control	Time in range	+ 1h 17 m	+ 2h 49m
	FPG (mg/dL)	-15.7	-21.4
	PPG (mg/dL)	-34.8	-41.0
	Severe hypoglycemia (per 100 PY)*	-2.0	-3.4
Other Benefits	SBP (mmHg)	-2.0	-3.5
	Body weight (kg)	-2.2	-3.0

*Risk Reference of EAIR, 52 week data

Additional DKA Risk Mitigation Measures: Beyond Clinical Trial Activities

More specific patient selection	▪ Willingness and ability to perform ketone monitoring. Strong T1D disease management understanding.

More specific ketone monitoring and mitigation instructions	▪ Start treatment only if values normal at baseline. Check after initiation of treatment
	▪ Assess ketones: e.g. with changes to diet or exercise, pump set changes or during acute illness
	▪ Hold Sotagliflozin:
	  ▪ If BHB between 0.6 to ≤ 1.5 or urine ketones = 1+ and symptoms
	  ▪ If BHB > 1.5 or urine ketone ≥ 2
	▪ Hydrate, take carbs, insulin and call doctor when holding Sotagliflozin

Insulin dose guidance	▪ Maintain Adequate insulinization ▪ Insulin dose reductions should be done cautiously to avoid ketosis and diabetic ketoacidosis
Extensive and specific risk communication	▪ Educate on risk, importance of ketone monitoring, mitigation ▪ Communication to prescribers, non-prescribers, and patients ▪ Publications

Phase 2 / 3 T1DM Studies: Treatment-Emergent Genital Mycotic Infections – Safety Population

Category	Placebo	Sotagliflozin 200 mg	Sotagliflozin 400 mg
Total	N=1324	N=559	N=1321
Female	N=672	N=274	N=660
Exposure-adjusted Incidence Rate (EAIR) per 100 Subject-years	6.4 (3.9, 8.9)	17.1 (11.9, 22.4)	22.3 (17.6, 26.9)
Male	N=652	N=285	N=661
Exposure-adjusted Incidence Rate (EAIR) per 100 Subject-years	1.2 (0.2, 2.3)	3.2 (1.0, 5.4)	5.8 (3.4, 8.1)

Phase 2 / 3 T1DM Studies: Summary of Characteristics of TEAE of GMI – Sex and Severity

Category	Placebo N=1,324	Sotagliflozin 200 mg N=559	Sotagliflozin 400 mg N=1,321
All GMI Events (subject, %, event)	30 (2.2) 45	49 (8.8) 61	111 (8.4) 173
Severe events	0	1 (0.1)	1 (0.1)
Male (subject, %, event)	5 (0.8) 6	8 (2.8) 9	23 (3.5) 29
Severe events	0	0	0
Female (subject, %, event)	25 (3.7) 39	41 (15.0) 52	88 (13.3) 144
Severe events	0	1 (0.4)	1 (0.2)

Absolute Risk of DKA: Consistent Rates of DKA Among SGLT Inhibitors in T1D Clinical Trials and Real World Data

	Approximate Events per 100 PY		
	T1D Clinical Trials	SENTINEL 2013-2018[3] (Broad – Narrow)	MarketScan in SGLT2 Inhibitors 2017
Sotagliflozin	3.6	N/A	N/A
Empagliflozin[1]	5.5	4.0 – 6.0	4.2
Dapagliflozin[2]	3.7	3.4 – 6.0	
Canagliflozin	N/A	4.7 – 7.9	

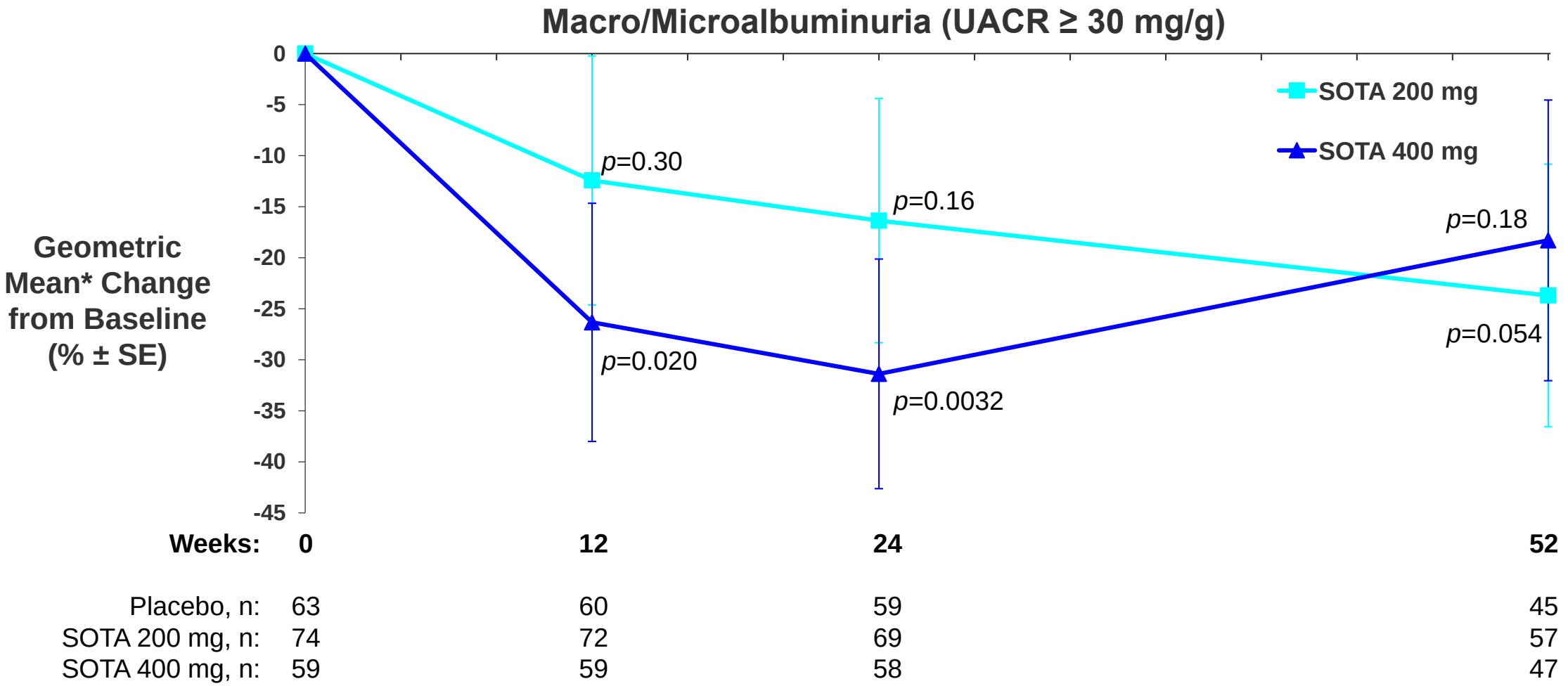
1. Diabetes Care, 2018 Oct; dc181749 (empagliflozin clinical trial); 2. Diabetes Care, 2018 Oct; dc181087 (dapagliflozin clinical trials); 3. Figure 32 FDA Briefing Doc

Total Hospitalizations – Severe Hypoglycemia and DKA

	Placebo Events / Patients	**All Sotagliflozin** Events / Patients
Total Hospitalizations (All Phase 3)	**62 / 1,229**	**126 / 1,748**
SH Hospitalizations (All Phase 3)	**8 / 1,229**	**6 / 1,748**
DKA Hospitalizations (All Phase 2/3)	**5 / 1,307**	**54 / 1,896**

- **Most severe hypoglycemia episodes occur outside of hospital**
- **Most DKA events require hospitalization**

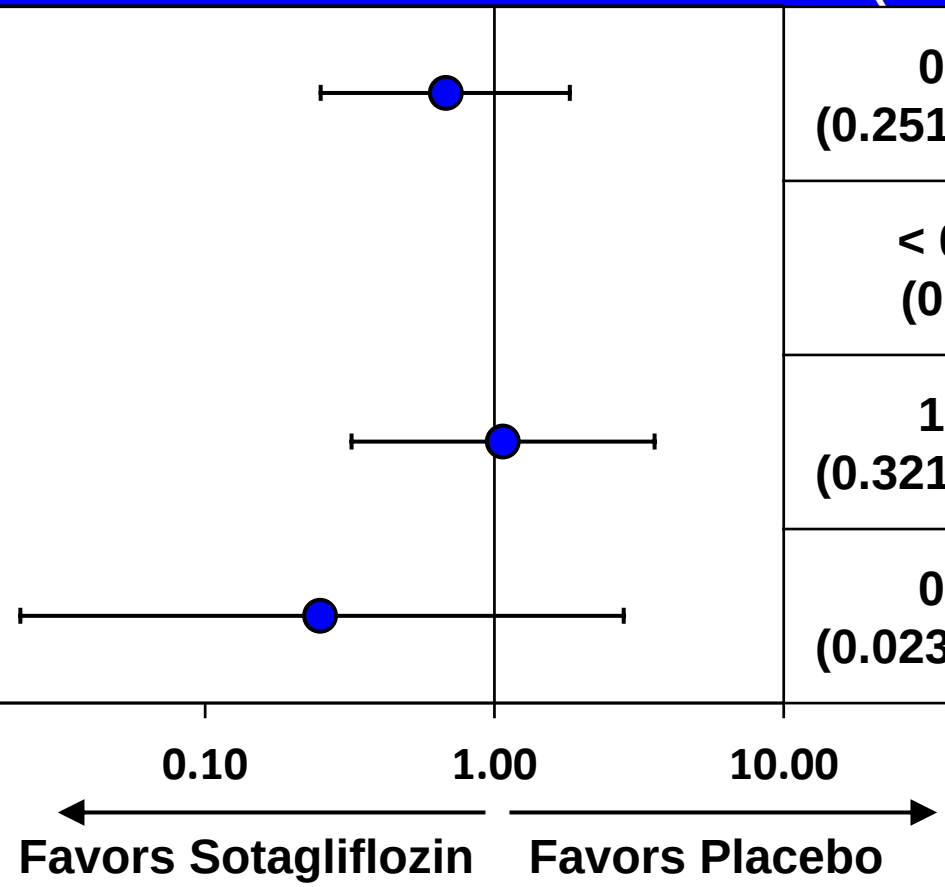
Pooled 309 / 310 (mITT): Placebo-Corrected UACR Percent Changes in Micro/Macroalbuminuria (≥ 30 mg/g)



*Geometric mean was estimated from MMRM model.

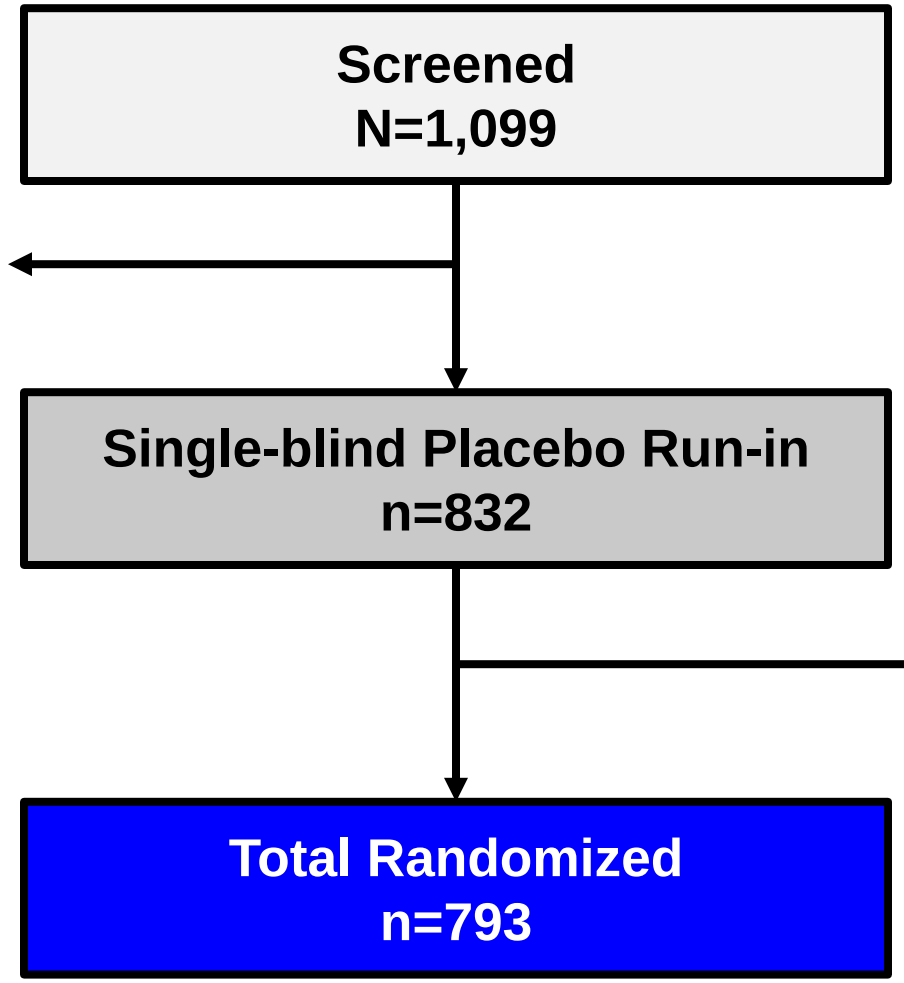
Phase 2 / 3 T1D and T2D Studies: Positively Adjudicated MACE

	All Sotagliflozin n / N (%)	Placebo n / N (%)	Hazard Ratio (95% CI)
MACE	9 / 1998 (0.45%)	7 / 1388 (0.50%)	0.68 (0.251, 1.822)
CV death	0	2 / 1388 (0.1%)	< 0.01 (0 , -)
Non-fatal MI including silent MI	8 / 1998 (0.40%)	4 / 1388 (0.28%)	1.07 (0.321, 3.577)
Non-fatal stroke	1 / 1998 (0.05%)	2 / 1388 (0.14%)	0.25 (0.023, 2.798)



Includes data from 7 completed T1D and T2D studies

Study 309: Enrollment Flow Diagram



Excluded* **n=267**

- Inclusion criteria not met n=149
- Exclusion criteria met n=68
- Patient decision n=39
- Consent withdrawn n=7
- Physician decision n=2
- Noncompliance n=2
- Sponsor decision n=1

Discontinued* **n=39**

- Patient decision n=14
- Exclusion criteria met n=10
- Inclusion criteria not met n=6
- Noncompliance n=5
- Physician decision n=2
- Consent withdrawn n=2
- Lost to follow-up n=1

***patients could be included more than once**

Improvement in DTSQs Individual Items

Individual DTSQs Items	Study 309			Study 310		
	Placebo N=268	200 mg N=263	400 mg N=262	Placebo N=258	200 mg N=261	400 mg N=263
How satisfied are you with your current treatment?	0.0 (1.39)	0.4 (1.24)	0.4 (1.14)	0.0 (1.21)	0.2 (1.24)	0.2 (1.24)
How often have you felt that your blood sugars have been unacceptably high recently?	0.1 (1.57)	-0.7 (1.53)	-0.7 (1.69)	0.0 (1.40)	-0.8 (1.66)	-0.7 (1.57)
How often have you felt that your blood sugars have been unacceptably low recently?	0.2 (1.54)	-0.2 (1.65)	-0.2 (1.42)	-0.1 (1.49)	-0.5 (1.51)	-0.3 (1.66)
How convenient have you been finding your treatment to be recently?	0.1 (1.40)	0.7 (1.23)	0.6 (1.25)	0.1 (1.20)	0.3 (1.45)	0.4 (1.24)
How flexible have you been finding your treatment to be recently?	0.2 (1.52)	0.6 (1.43)	0.4 (1.34)	0.1 (1.17)	0.5 (1.23)	0.3 (1.31)
How satisfied are you with your understanding of your diabetes?	0.0 (0.88)	0.3 (0.89)	0.3 (0.90)	0.0 (0.93)	0.3 (1.03)	0.3 (1.04)
Would you recommend this form of treatment to someone else with your kind of diabetes?	-0.4 (1.29)	0.2 (1.09)	0.2 (1.09)	-0.1 (1.02)	0.3 (1.40)	0.2 (1.15)
How satisfied would you be to continue with your present form of treatment?	-0.3 (1.26)	0.3 (1.15)	0.3 (1.08)	-0.2 (1.08)	0.3 (1.15)	0.2 (1.10)

Mean (SD) change from baseline to week 24; no p-values reported for single item change scores

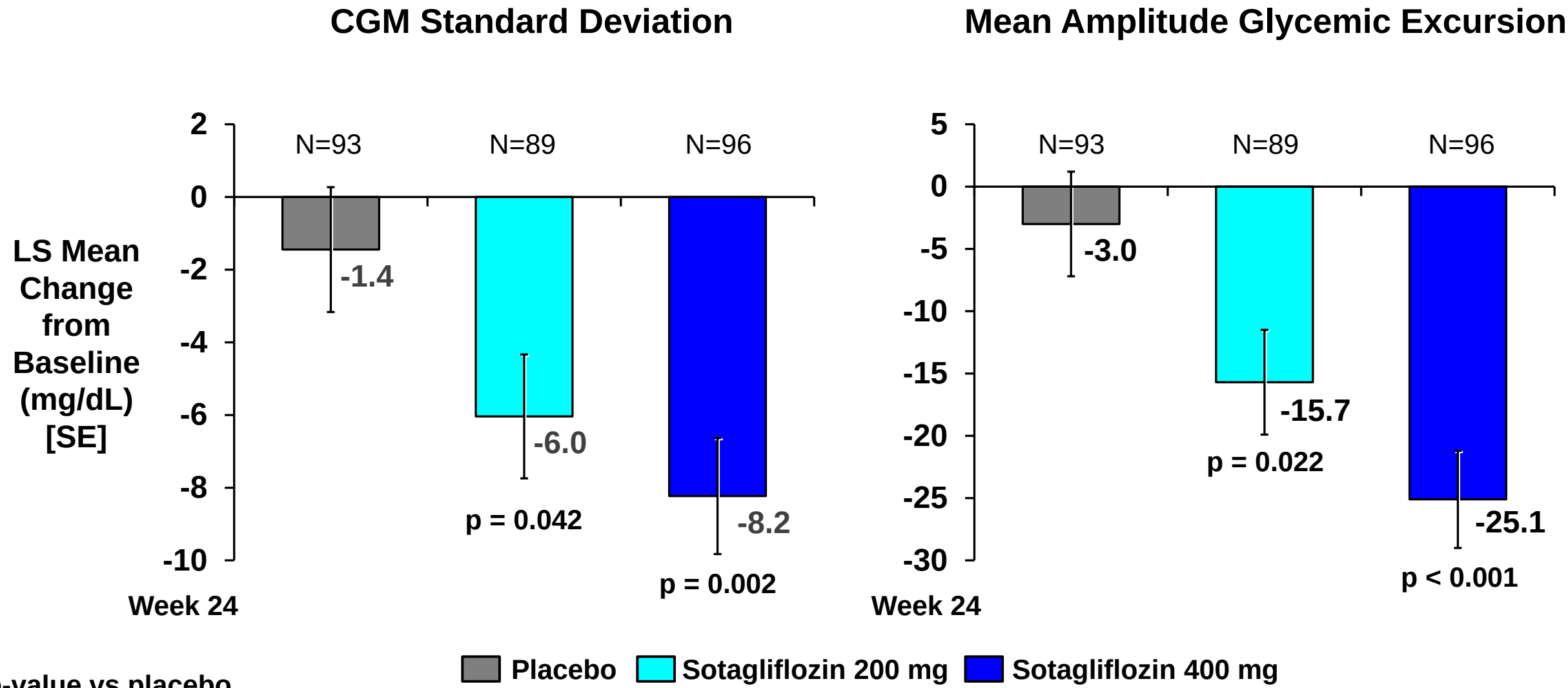
A1c Effect on Microvascular Disease Risk and Sotagliflozin Effect on Death due to SH and DKA

Morbid Complications	Incidence per 10,000 PY	Potential % Reduction	Event Difference per 10,000 PY
Microvascular complications[1]			
Retinopathy	225	20%	-45
Neuropathy	412	20%	-82
Renal disease*	233	20%	-47
Decrease in Severe Hypoglycemia Death[2]	3 to 6	24 to 41%	-1 to -2
Increase in DKA Death	N/A	N/A	0 to +1

*Persistent albuminuria ≥ 40 mg per 24 hours

1. DCCT
2. Swedish and Norwegian National Registry

Pooled 309 / 310 CGM Sub-Study: Dose Related Improvements in Glucose Variability



Pooled 309 / 310: Documented Hypoglycemia by Time of Day

Documented Hypoglycemia Event Rate (events/patient/year)	Placebo N=526	Sotagliflozin 200 mg N=524	Sotagliflozin 400 mg N=525
Documented Hypoglycemia ≤ 70 mg/dl			
Overall Event Rate	95.6	81.3	83.7
Diurnal Event Rate	83.9	70.6	72.9
Nocturnal Event Rate	12.2	11.0	11.1
Documented Hypoglycemia ≤ 55 mg/dl			
Overall Event Rate	19.0	14.9	15.0
Diurnal Event Rate	16.3	12.6	12.7
Nocturnal Event Rate	2.7	2.3	2.3