NHLBI-Duke Collaboratory Grand Rounds

The Next Generation of Patient-Centered Trials – No site visits, home-delivery of meds and patient-reported outcomes – The CHIEF-HF Trial

John Spertus

Lauer/Missouri Endowed Chair and Professor, UMKC

Clinical Director of Outcomes Research

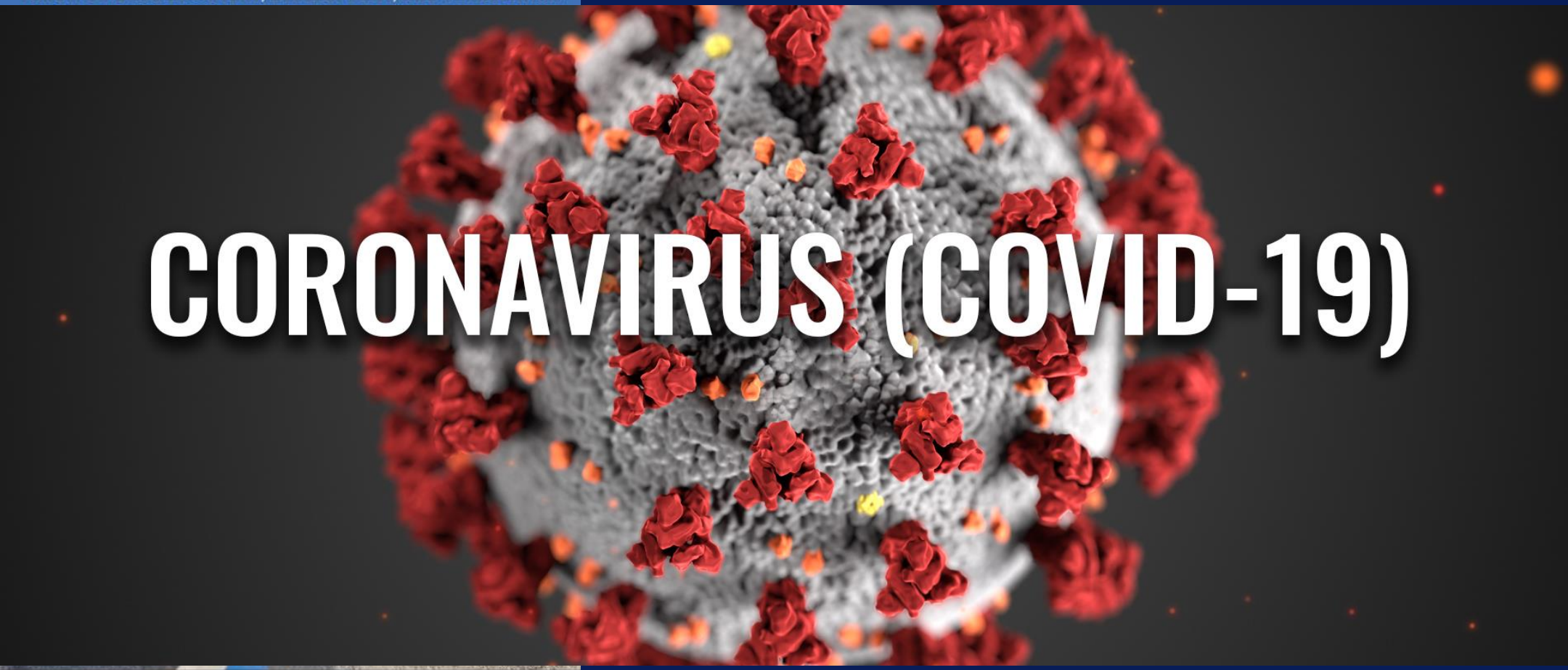
Saint Luke's Mid America Heart Institute

Disclosures

- CHIEF-HF sponsored by: Janssen Scientific Affairs
- Speakers Bureaus: None
- Grant Support: ACCF, Myokardia, Janssen, Abbott Vascular
- Consultant: United Healthcare, Bayer, Novartis, Merck Janssen, Myokardia, Pfizer, BCBS of KC
- Copyrights/Patents: SAQ, KCCQ, PAQ

Clinical Trial Challenges – 2012 IOM Report

FORUM ON DRUG DISCOVERY, DEVELOPMENT, AND TRANSLATION



WORKSHOP SUMMARY

INSTITUTE OF MEDICINE
OF THE NATIONAL ACADEMIES

Traditional RCTs show SGLT2i's are Effective in Heart Failure

- Improve survival and lower hospitalization…
  - HFrEF: DAPA-HF, EMPEROR-Reduced, SOLOIST-WHF
  - HFpEF: EMPEROR-Preserved
- Evolving understanding of Health Status benefits…
  - HFrEF: DAPA-HF, DEFINE-HF, EMPEROR-Reduced
  - HFpEF: EMPEROR-Preserved, PRESERVED-HF
- Canagliflozin has established benefits for…
  - Reducing adverse ASCVD and HF outcomes in patients with diabetes
  - Renal protection in patients with diabetes
  - Not approved for a HF indication

Treatment Goals for Heart Failure

Principal Treatment Goals

To Make Patients

To Make Patients

Research Question:

Does 100 mg/d of canagliflozin improve the symptoms of patients with heart failure after 12 weeks of treatment?

Arrhythmias | Heart Failure Admissions

Mortality

Symptoms | Functional Status

Quality of Life

Evolutions in FDA Views on HF Trials

An official website of the United States government Here's how you know

U.S. FOOD & DRUG ADMINISTRATION

Home / Drugs / DDT COA #000084: Kansas City Cardiomyopathy Questionnaire (KCCQ)

DDT COA #000084: Kansas City Cardiomyopathy Questionnaire (KCCQ)

Share | Tweet | Linkedin | Email | Print

Drugs

- Regulatory Science Research and Education
- Development & Approval Process | Drugs
- Drug Safety and Availability
- Emergency Preparedness | Drugs
- Guidance, Compliance, & Regulatory Information
- News & Events for Human Drugs
- Resources for You | Drugs
- Science and Research | Drugs

Clinical Outcome Assessments (COA) Qualification Submissions
Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)
Division of Cardiovascular and Nephrology (DCN)

DDT COA Number
DDT COA #000084

Instrument Name
Kansas City Cardiomyopathy Questionnaire (KCCQ)

Disease/Condition
Heart Failure (HF)

Concept of Interest
HF symptoms and their impact on physical limitations

Context of Use
Patients with HF

COA Type
PRO

Qualification Stage
Qualified

Content current as of:
04/16/2020

Regulated Product(s)
Drugs

Topic(s)
Drug Development Tools

The KC Cardiomyopathy Questionnaire

- 23/12 items that measure 5 clinically relevant domains
  - » Physical Limitation
  - » Symptoms
    - Frequency
    - Severity

    Total Symptom Score
  - » Social Limitation
  - » Quality of Life
- Represents the *patient's* perspective of their HF
- Available in over >100 translations
- Qualified by FDA (CDRH & CDER) as a COA
- *Can be collected virtually!!*

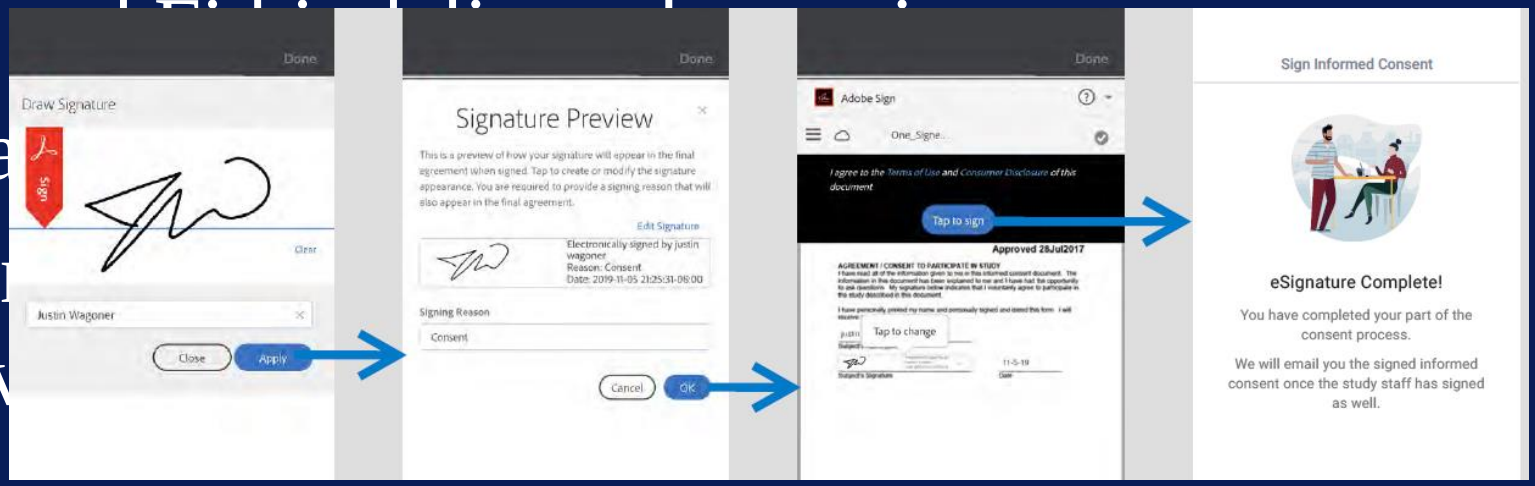
Green et al, JACC 2000; 35:1245-55

Computerized Phenotype to Screen Patients

- Inclusion Criteria
  - Confirmed HF of any type (based on EHR review)
  - Sole access to iPhone (6 or later) or Samsung S7 (or later)
  - Willing to wear a Fitbit (Versa 2)
  - Screening KCCQ Overall Summary Score ≤ 80
- Exclusion Criteria
  - Concurrent use of an SGLT2i
  - History of diabetic ketoacidosis
  - Type 1 diabetes
  - eGFR<30 ml/min

Conduct of the CHIEF-HF Study

- Sites screened EMR for potential patients
  - Patients invited by email, portal, phone, or at visit
- Patients went to website to learn of trial
  - If interested, they opted in to be screened
- If eligible, app downloaded & eConsent obtained by PI
- Study Meds
- 12-week trea
- Planned to e
  administrativ

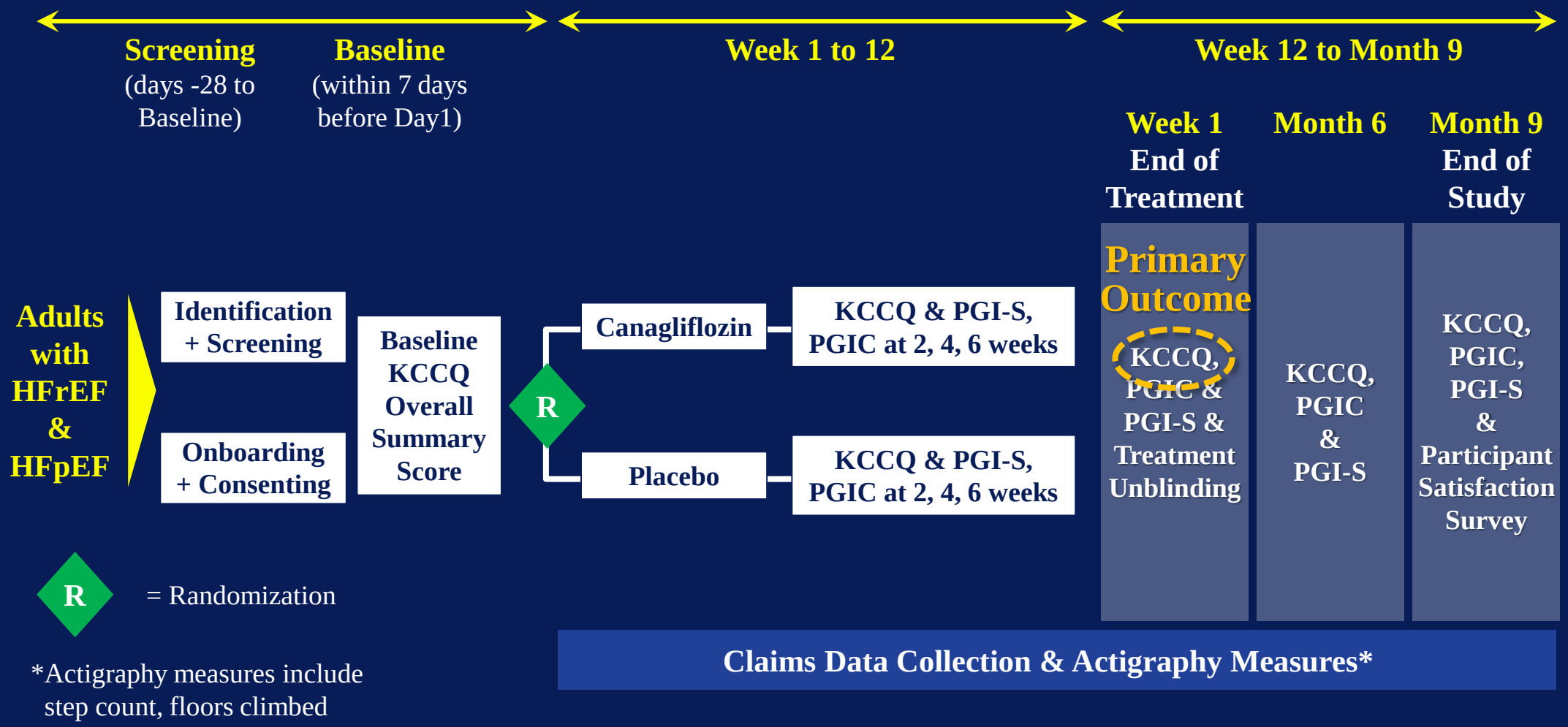


News…


Faith Family Friends
ANNA MEADOWS
DRUG TRIAL PARTICIPANT
CORONAVIRUS
IMPACT
abc
KMBC
-1:27

An RCT without a Face-to-Face Visit

CHIEF-HF Study Schematic



*Actigraphy measures include step count, floors climbed

Spertus, J.A., *et al.* Novel Trial Design: CHIEF-HF. *Circ Heart Fail* **14**, e007767 (2021)

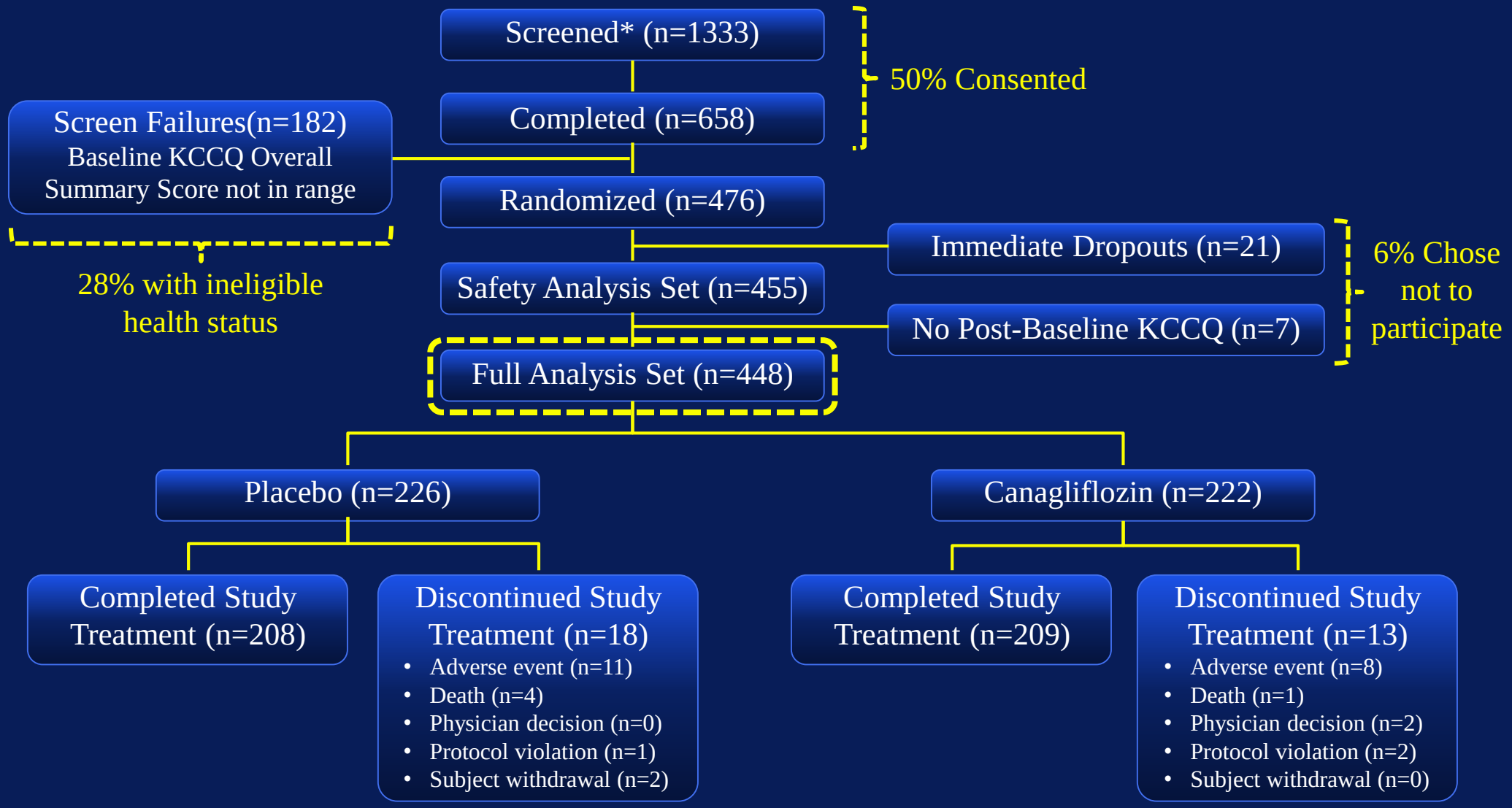
Data Sources

- Enrolling Site –
  - Patient Characteristics:
    - » Age, gender, race, EF category, diabetes status
- Study App collected Outcomes –
  - KCCQ and Fitbit through app
  - Self-reported compliance
- Claims Data –
  - Confirmation of eligibility
  - Adverse events
  - Concurrent meds before and after study

Analytic Approach

- Primary Outcome – 12-Week Change in KCCQ TSS
  - Conducted on all participants with ≥ 1 dose of study medication and completing ≥1 post-randomization KCCQ
- Analytic approach
  - Primary – Mixed effect model for repeated measures
    - » Included treatment, stratification (HFrEF vs. HFpEF), baseline KCCQ, time and time x treatment interaction
  - To support interpretability, a responder analysis conducted
  - Subgroup comparison by type of HF (HFrEF vs. HFpEF) and diabetes status

Consort Diagram



*Visited website then screened as eligible by Site PI

Baseline Characteristics Well Balanced

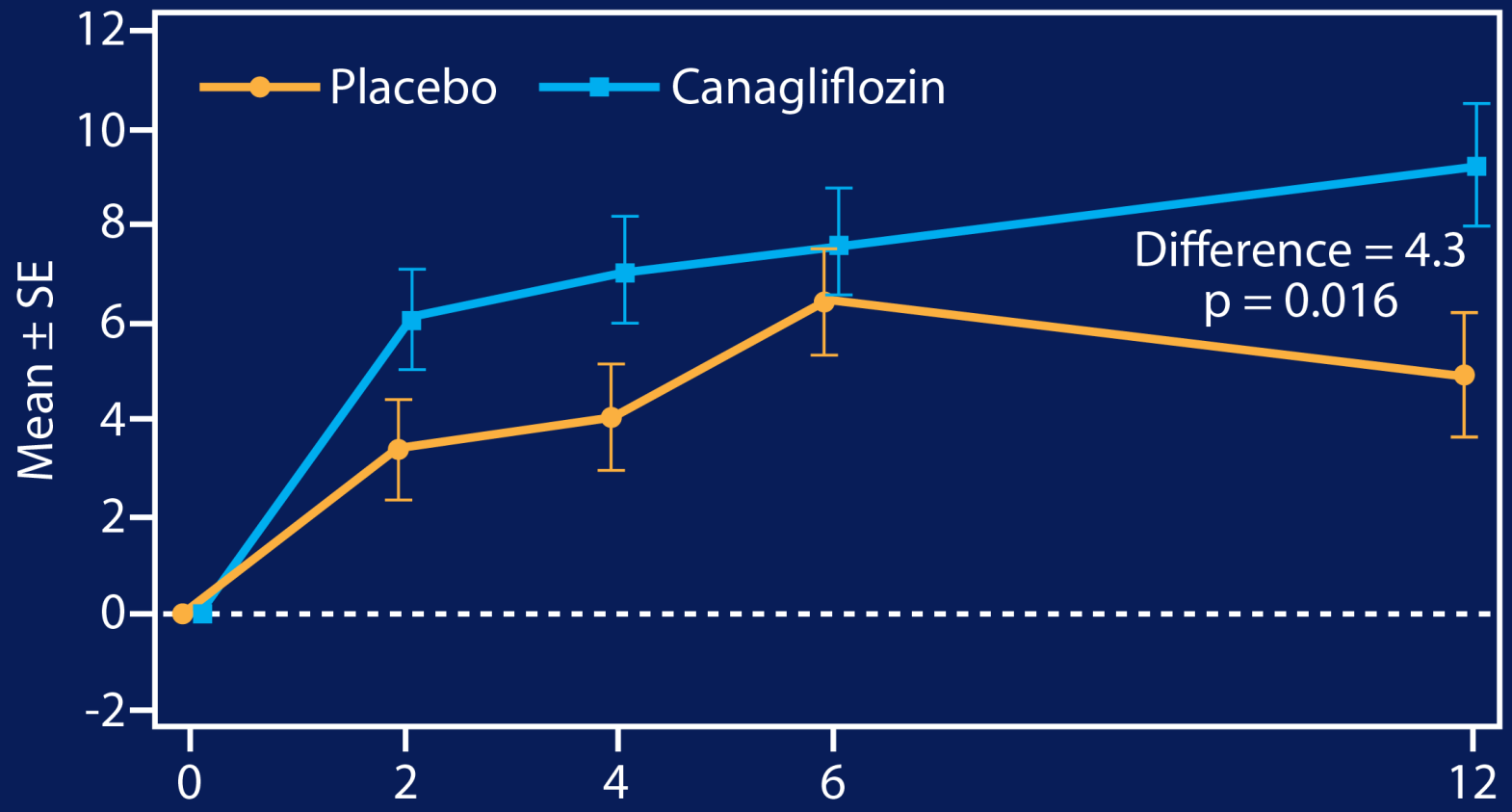
	Placebo	Canagliflozin
Sample size	226	222
Age (years)		
Mean (SD)	64.0 (13)	62.9 (13)
Median	66.0	65.0
Range	22 to 94	20 to 89
18-25	2 (0.9%)	4 (1.8%)
26-50	38 (16.8%)	35 (15.8%)
51-64	59 (26.1%)	68 (30.6%)
≥65	127 (56.2%)	115 (51.8%)
Female Gender	97 (42.9%)	104 (46.8%)
Race		
White	194 (85.8%)	182 (82.0%)
Black or African American	30 (13.3%)	35 (15.8%)
Asian	1 (0.4%)	1 (0.5%)
Other	1 (0.4%)	4 (1.8%)
Type 2 Diabetes Mellitus	59 (26.1%)	66 (29.7%)
Non-Type 2 Diabetes Mellitus	167 (73.9%)	156 (70.3%)
Randomization Stratification: HFpEF	135 (59.7%)	132 (59.5%)
Randomization Stratification: HFrEF	91 (40.3%)	90 (40.5%)
KCCQ Total Symptom Score	58.0 ± 21.1	57.4 ± 21.3
KCCQ Overall Summary Score	52.7 ± 18.3	51.6 ± 18.8
KCCQ Clinical Summary Score	56.3 ± 19.5	54.6 ± 19.7
KCCQ Physical Limitation Score	54.4 ± 21.5	51.9 ± 21.2
KCCQ Social Limitation Score	50.9 ± 22.4	50.9 ± 23.8
KCCQ Quality of Life Score	47.4 ± 21.8	45.8 ± 21.2

- Median Age = 65
  - Range = 20 to 94
- 14% Black or AA
- 45% women
- 59% HFpEF
- 72% w/o diabetes

Success of Study Execution

	Collected/Confirmed	Expected	Rate
Participant Eligibility			
Claims validation of HF at Baseline	448	448	100%
Study Drug Delivery and Adherence			
Direct to patient drug delivered	448	448	100%
Self-reported medication compliance ≥80%	385	426	91%
Data Collection			
eDiary compliance ≥ 80%	426	448	95%
KCCQ at 2 weeks	444	448	99%
KCCQ at 4 weeks	431	438	98%
KCCQ at 6 weeks	418	429	97%
KCCQ at 12 weeks	414	422	98%
Fitbit data compliance ≥ 80%	422	448	94%

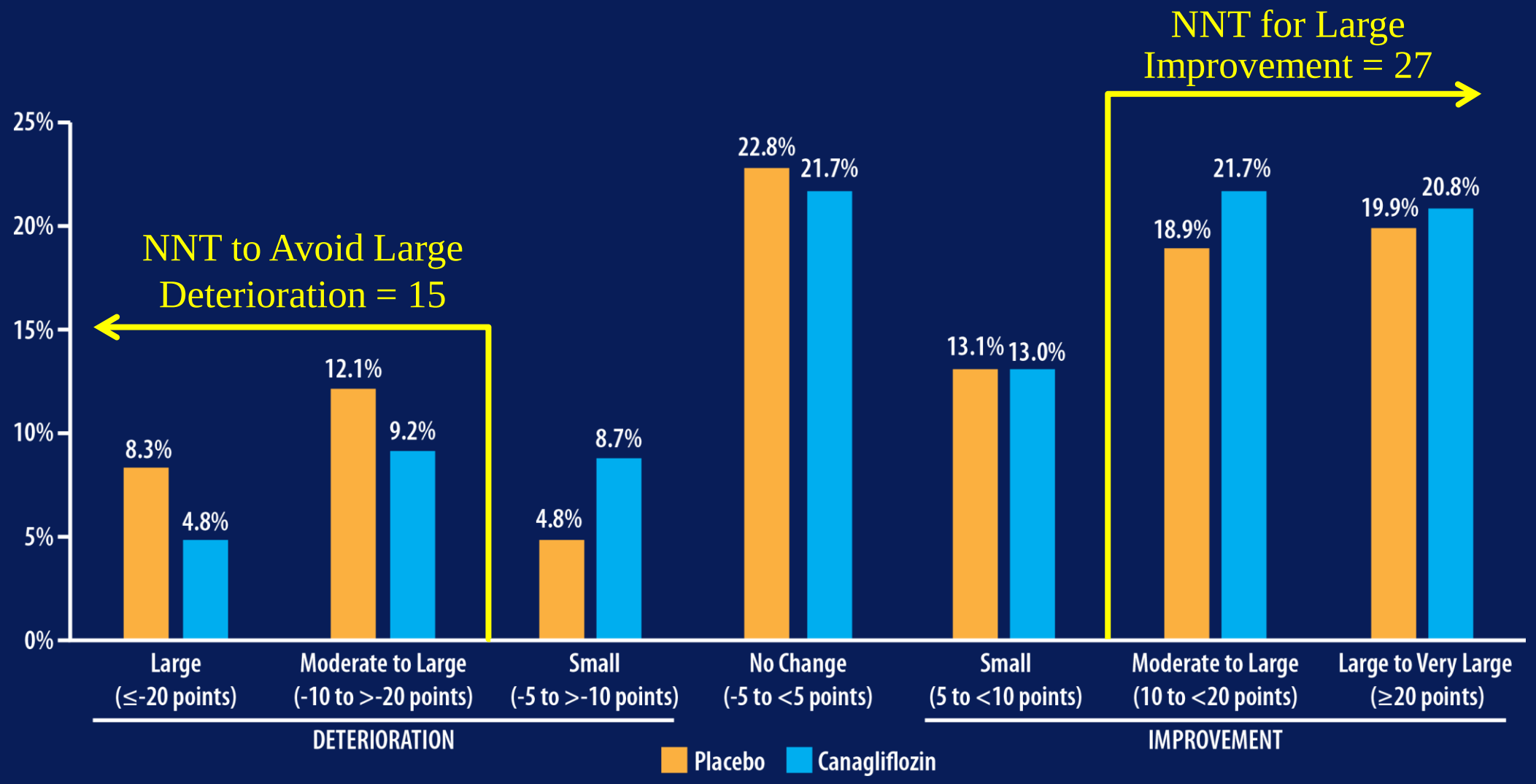
Primary Results – KCCQ Total Symptom Score



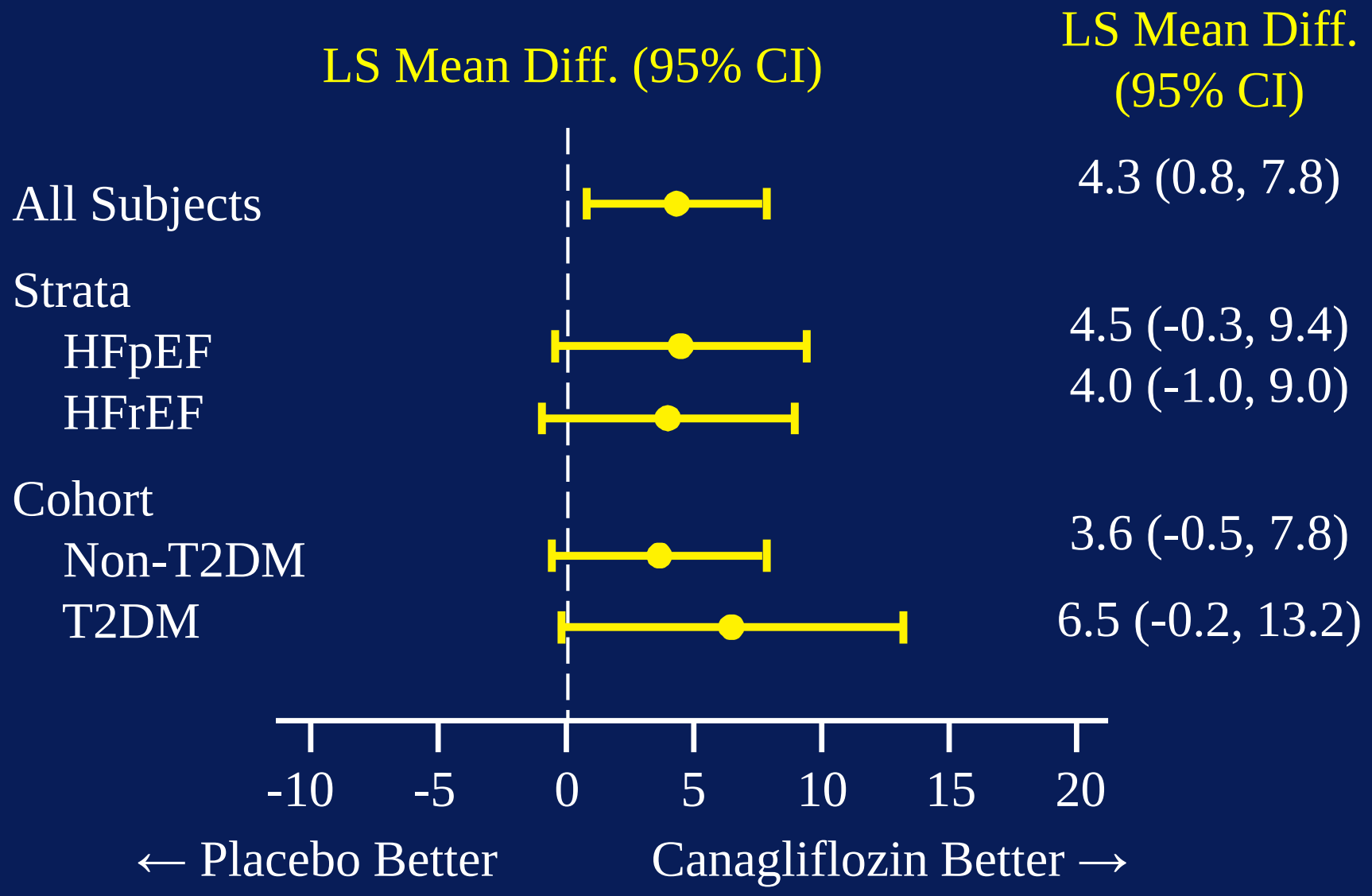
Number of Subjects					
Placebo	226	222	215	209	206
Canagliflozin	221	221	215	208	207

Primary Results – KCCQ Total Symptom Score

Magnitudes of Clinical Change in KCCQ Total Symptom Score Over 12 Weeks



Consistent Benefit in All Subgroups



No New Safety Concerns Identified

Overall Summary of Post-randomization Adverse Events Through Week 12 As Reported in Claims Database

	Placebo	**Canagliflozin**
Number of participants	231	224
Serious adverse events	18 (7.8%)	27 (12.1%)
Death	4 (1.7%)	2 (0.9%)
By Cohort		
T2DM	3 (1.3%)	1 (0.4%)
No T2DM	1 (0.4%)	1 (0.4%)
By Strata		
HFrEF	3 (1.3%)	2 (0.9%)
HFpEF	1 (0.4%)	0

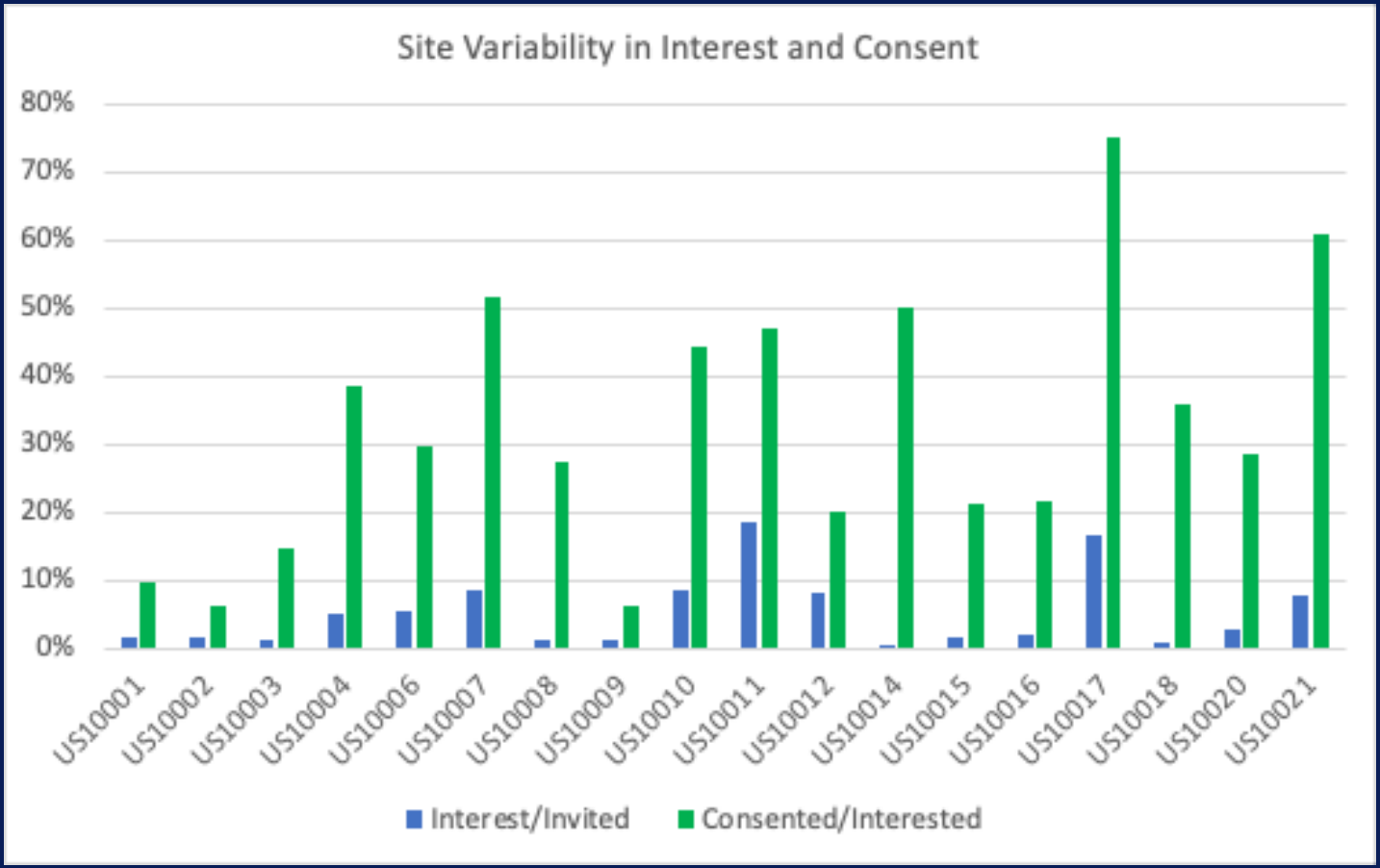
Serious adverse event numbers are from hospitalization/emergency room visits w/in 120 days
Death numbers are from Disposition data including records up to 30 days after end of treatment

Limitations

- Reduction in planned sample size
  - The sponsor stopped the study for shifting priorites
    - » Done before database lock and unblinding
  - Effect size was strong enough to still define benefit
- Conducted during Covid-19 Pandemic
  - May have altered participants' usual activities
- Short-term study focused on symptoms
  - Not powered for clinical events
- Study design required access to a smartphone
  - Potential SES biases, but access to smartphones is increasing

Variability in Site's Recruitment

- Invites:
  - 172 to 46,000
- Screened:
  - 2 to 498
- Consented:
  - 1 to 417
- Randomized:
  - 1 to 173



More Personalized Strategies – targeted portal messages, personal emails and phone calls – a were more successful thank mass emails or snail mail

Other Pearls Acquired…

- The Technology is Critical
  - Ideally accessible from all smart devices
  - Evolving platforms (e.g. Hugo) can collect data & outcomes
- Defining Data Needs is Critical
  - If you really need it, collect it at baseline or through app
- Virtual Support Centers are Exceedingly valuable
  - Troubleshooting patient/tech issues
- Regulatory Departments need to Evolve on Consent
- As in all Trials, motivated PIs worth their weight in gold

Conclusions

- Canagliflozin 100mg daily improved HF symptoms
  - Regardless of EF or diabetes status
  - Effects observed as early as 2 weeks, sustained to 3 months
  - Started without any patient visits or labs
- Models a new approach to the conduct of RCTs
  - More rapid enrollment and completion than traditional RCTs
  - Addresses many of the Institute of Medicine's Challenges to improving clinical trials
- *Launched the week of US shutdown due to Covid-19 and completed during the pandemic*

Questions

Thank you…

- Janssen for sponsoring the study
- PRA for partnering, creating the mobile health platform & app, and supporting access to claims data
- Site investigators for embarking on a novel RCT
- Participants for engaging in a study to understand the impact of SGLT2 inhibitors on their symptoms
- Kensey Gosch for statistical validation of study findings