ITCA 650

Intarcia Therapeutics (Business Unit of i2o Therapeutics)

Endocrinologic and Metabolic Drugs Advisory Committee

Sept 21, 2023

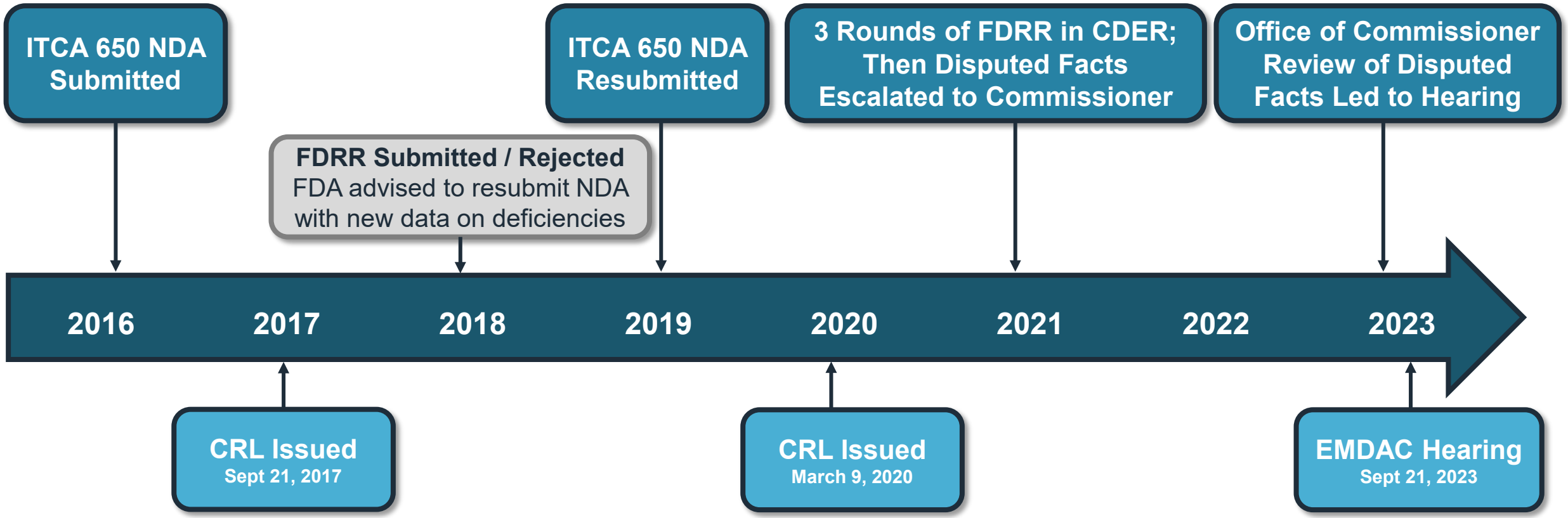
ITCA 650

Intarcia Therapeutics

Kurt Graves

Chairman, President & CEO

Commissioner's Office and FDA Chief Scientist Granted this Hearing After Review of Issues of Fact from Intarcia vs CDER's Denial Issues[1]



1. CDER's Proposed Order to Deny ITCA 650 Outlining 6 Prioritized Issues on Federal Docket

CRL = complete response letter; FDRR = Formal Dispute Resolution Within CDER

Today's EMDAC is a Critically Important Opportunity to Review Objective Data and Resolve Disputed Facts

- EMDAC to advise The Office of the Commissioner and FDA's Chief Scientist Dr. Bumpus who determined a hearing to review factual disputes was warranted

FDA's Chief Scientist wrote[1]:
"I have identified numerous disputes between the parties…
I believe that a public hearing before an advisory committee could aid in the resolution of the parties' disputes and enable the Office of the Commissioner to render a final decision."

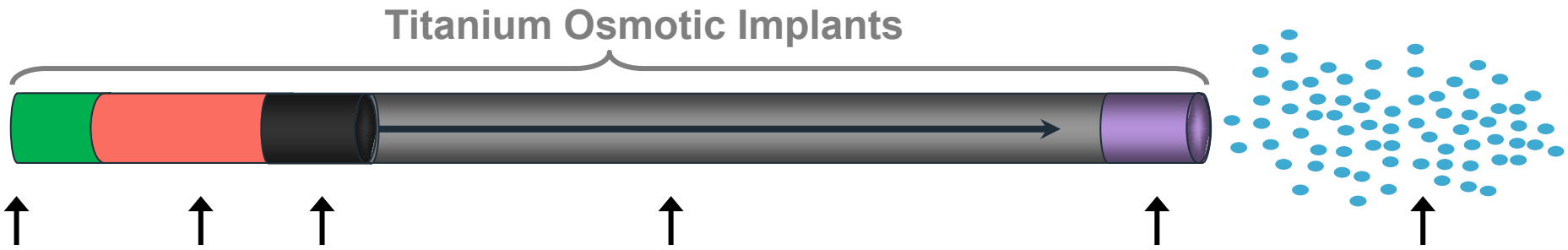
1. Letter from FDA's Chief Scientist / OC Granting Intarcia an Alternate Form of a Public Hearing Before the EMDAC (Feb 8, 2023)

ITCA 650 Delivers Exenatide With Twice-Yearly Dosing: Already Approved GLP-1 for Treatment of T2DM

Exenatide Brand Names	Self-Injection Administration	Approval Year
Byetta®	Twice-daily injections	2005
Bydureon®	Once-weekly injections	2012

- One of the only GLP-1s potent enough to fit into a once or twice-yearly implant
- Proven efficacy in reducing HbA_{1c}
- Well understood MoA and clinical pharmacology
- Well characterized safety profile; including CV safety from large/long CVOT
  - Main side effects transient GI AEs at dose initiation/escalation (a class effect)
  - **Exenatide has GLP-1 labeled Warnings for AKIs associated with GI AEs**

ITCA 650 Delivers Exenatide Twice-Yearly Using Well Established DUROS* Osmotic Implants with Fail-Safe Against Bolus Release



Intake membrane fail-safe designed to withstand 710 psi

If pressure inside implant exceeded that level, fail-safe design would cause intake membrane to back out - renders a static device with DM in place

DM has psi fail-safe that prevents DM from dislodging from implant's drug reservoir

DM withstands ≥ 6400 psi (~10x higher than psi required to dislodge intake membrane)

Fail-safe makes intake membrane back out first rendering a static device, no risk of bolus release

*DUROS implants previously approved as Viadur for prostate cancer; marketed for years until sponsor exited therapy area

To Address CDER's Issues we will Provide Data Supporting Benefit-Risk and that ITCA 650 is In-Line with GLP-1 Class

Positive Benefit-Risk for ITCA 650	ITCA 650's Safety Profile In-Line with GLP-1s and Labeled Warnings
Need for extended maintenance dosing options to help address crisis in HbA1c control and adherence	**GI AEs at dose initiation and escalation most common and in-line with GLP-1s; no new signals**
4 positive phase 3 trials all met endpoints with unequivocal efficacy and twice-yearly dosing	**GI AEs associated with Serious AKIs (a class effect)** All GLP-1s have post-marketing AKI SAEs with GI AEs RCTs with AKI imbalances linked to GI AEs[2]
Overall SAEs and deaths comparable to placebo[1] SAEs: 14% vs 14% Deaths due to AEs: 2% vs 2%	**Cross-trial comparisons of pre- vs post-approval CVOTs are scientifically unsound** Study 107 met FDA's pre-approval CVOT primary endpoint; GLP-1 CV harm lacks biologic plausibility

1. ISS Section of ITCA 650 NDA; 2. First 3 GLP-1 CVOTs with AKI SAE imbalances in 2017; further GLP-1s imbalance in AKI SAE risk seen RCTs in expanding populations (e.g. semaglutide in STEP-2, STEP-HFpEF); CVOT = Cardiovascular Outcomes Trials; RCT = Randomized & Controlled Trials

Per Regulations, Hearing Granted by Commissioner's Office to Resolve Issues of Fact Submitted vs. CDER's 6 Denial Issues

CDER's Proposed Denial Case[1] has 6 Issues Under Factual Dispute
Efficacy is Not Disputed

Clinical Safety Main Focus

1. AKI SAE imbalance and deaths isolated to ITCA 650
2. CV assurance from pre-approval CVOT
3. Clinical validation of implants
4. Device reliability
5. Sterility
6. Quality controls

Implants / CMC Secondary

1. CDER's Official Proposed Denial Order with 6 Issues Outlined on Public Record / Federal Register on Sept, 2, 2021

Crux of CDERs AKI Position: GLP-1 Class Has No Proven Risk Of Serious AKI In Clinical Trials – Asserts AKI Is Isolated To ITCA 650

1) Division Asserts[1] there is no evidence the GLP-1 Class has any increased AKI Risk (imbalances in RCTs)

> "The distinction between ITCA 650 and other GLP-1s is that an AKI numerical imbalance was not evident in any other GLP-1 RCTs."[1]

2) Division Asserts[1] small numeric AKI imbalance in RCT Isolated to ITCA 650 to reject it

> "While we recognize that AKI is a labeled potential serious risk for the class, this specific risk was not identified from pre-marketing clinical trial data in other large GLP-1 RA programs"[1]

Evolving Facts In More RCTs Do Not Support CDER's Position of No Proven AKI Risk for GLP-1 Class

1. Division & OCHEN's Dr. Ellis Unger's Formal Dispute / FDRR Denial Letter 7-30-20; 2. CDER EMDAC Briefing Book

Evolution of GLP-1 RCT Data Shows On Treatment Imbalances in GI AEs and AKI SAEs are a Class Effect – with Clear Biologic Plausibility

(2009) 1st GLP-1 AKI Warning
Post-Marketing Reports Exenatide

(2017) All 3 Applications had AKI Imbalances
2 Approved with AKI Warnings; ITCA 650 Rejected

(2021 - 2023) AKI Imbalances Caused New AKI Warning
1st AKI Warning with "AKI Occurred In Clinical Trials"

2017 → 2021 → 2023

LEADER CVOT
Liraglutide[1]
N = 9340

Total AKI SAEs
164 drug vs
153 placebo
3.0% drug vs 2.9%*

AKI SAEs Death[1]
11 drug vs
5 placebo

Study 107 CVOT
ITCA 650
N = 4156

Total AKI SAEs
11 drug vs
4 placebo
0.5% drug vs 0.2%*

AKI SAE Deaths
0 drug vs
2 placebo

SUSTAIN-6 CVOT
Semaglutide[2]
N = 3297

Total AKI SAEs
30 0.5mg drug vs
18 0.5mg placebo
3.1% drug vs 2.2%*

AKI SAEs / Deaths
3 drug
(placebo dosing NA)

STEP-2
Semaglutide 2.4mg[3]
N = 1207

Total AKI SAEs
3 drug vs
1 placebo
0.5% drug vs 0.2%*

Non-serious AKIs Reported of 5 (1.0%) vs. 2 (0.5%)

NDA Trial in Obesity + T2D

STEP-HFpEF
Semaglutide 2.4mg[4]
N = 529

Total AKI SAEs
6 drug vs
2 placebo
1.9% drug vs 0.4%*

Trial in Obesity + HF

1. FDA & Sponsor's AKI SAEs in EMDAC Materials (p. 75 of 95); 2. Sponsor's Sustain-6 AKI SAEs listed on ClinicalTrials.gov months after EMDAC/approval
3. FDA Medical Review Data Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215256Orig1s000MedR.pdf
4. NEJM: Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity: https://www.nejm.org/doi/full/10.1056/NEJMoa2306963?logout=true

*% Patients with AKI SAEs

FDA's Chief Scientist Granted this Hearing Based on Identifying Numerous Disputed Facts vs CDER's 6 Issues

CDER's 6 Issues	Correct NDA Facts For ITCA 650
1. AKI SAE imbalance and deaths isolated to ITCA 650	▪ **Not 16 cases; only Study 107 had on-treatment AKI SAE imbalance: 11 (0.5%) vs 4 (0.2%)** ▪ **No AKI SAE deaths; no increase in dialysis; only 2 AKI SAE deaths on placebo** ▪ **CDER omitted serious AKI imbalances in other GLP-1 CVOTs by omitting repeat AKIs, post-hoc pooling of AKI SAEs, and using non-MedDRA proteinuria events (not AKI SAEs)**
2. CV risk assurance from pre-approval CVOT	▪ **Pre-approval CVOT met FDA primary endpoint required to bridge to post-approval CVOT** ▪ **No definitive and/or biologically plausible evidence of exenatide/GLP-1s causing CV harm**
3. Clinical Validation of IVR specs	▪ **4 successful phase 3 trials met endpoints; > 22,000 implants performed as designed** ▪ **Clinical validation of IVR specifications limits as effective & safe for the intended use**

CVOT protocol defined "on treatment"/treatment emergent as the time from the first implant to last implant removed; End of therapy (EOT) was 4 weeks from last implant removed

FDA's Chief Scientist Granted this Hearing Based on Identifying Numerous Disputed Facts vs CDER's 6 Issues

CDER's 6 Issues	Correct NDA Facts For ITCA 650
4. Device reliability and mitigation	▪ **DUROS implants previously approved, further improved with dFMEA risk mitigations** ▪ **Implants performed within pre-specified in-vitro release (IVR) upper and lower limits**
5. Sterility	▪ **CDER's briefing document notes sterility "deficiencies remain unresolved" that led to a clinical hold in 2017. This and prior assertions are false.** ▪ **FDA's 2020 Official EIR Report: FDA's lead pre-approval manufacturing inspector wrote:** ➢ "I reviewed the sterility failures investigations for the sterility failures that occurred in 2017 and led to the clinical hold being placed on the firm. I reviewed all investigation conducted at Catalent and Intarcia. The investigation appeared to be completed (See Exhibit UL-38). Raw data were reviewed. CAPA taken to address the clinical hold were reviewed and found to be acceptable. **No {sterility} deficiencies were noted.**"
6. Quality controls device filling and sterility tests	▪ **Controls in place; no empty implants in thousands of IVR tests, nor any clinical reports** ▪ **Passed all manufacturing sterility tests (PSTs) for phase 3 program; FDA has PST facts**

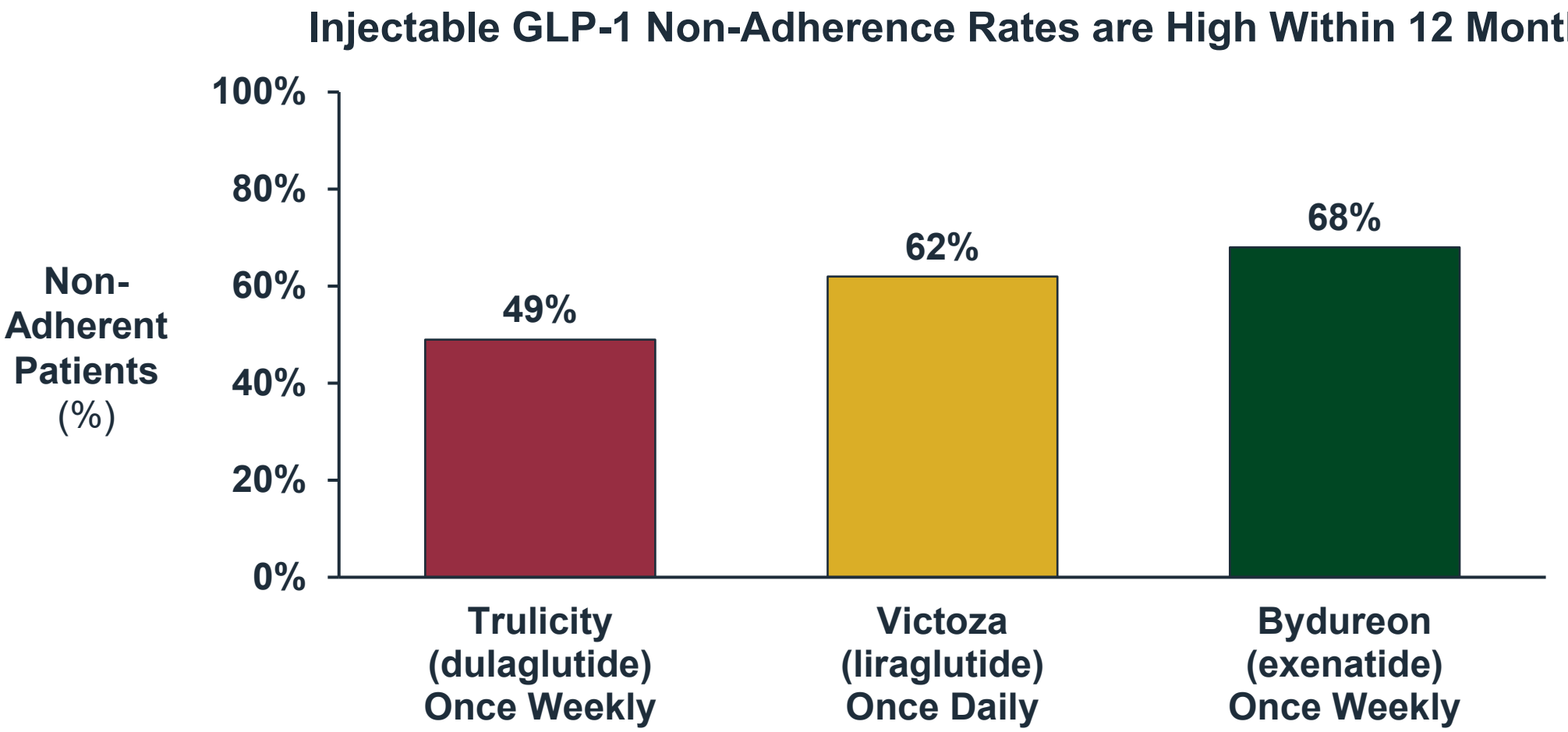
ITCA 650 – An Important GLP-1 Maintenance Therapy Option

ITCA 650: Twice-Yearly Dosing Designed to Help Address Poor HbA_{1c} Control and Poor Adherence Impacting Millions

- > 45 new T2DM tablets and injections approved in US over last 15 years[1]
- ≥ 50% of T2DM patients remain not at target HbA_{1c} levels of < 7%, largely due to poor adherence (taking > 80% of prescribed medication)
  - > 30% patients in US have chronic HbA_{1c} > 9%[2-6]
- Patients and doctors need new extended maintenance dosing options

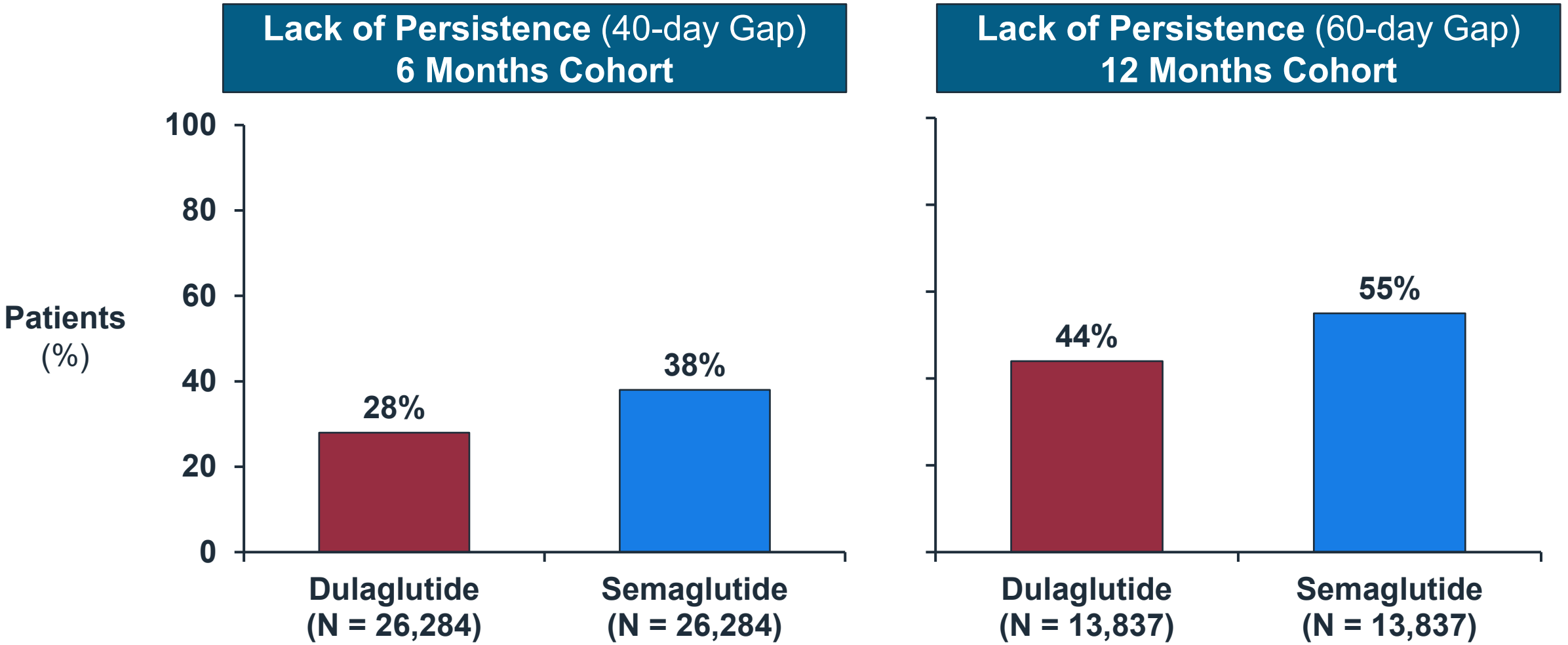
1. FDA Type 2 Diabetes US Drug Approvals: 2007-2022; 2. NEJM Diabetes Treatment And Control Trends 1999-2018, 2021; 3. National Committee for Quality Assurance, 2023; 4. International Diabetes Foundation. IDF Atlas; 5. Reuters Investigates USA Diabetes Special Report, 2021; 6. Type 2 Diabetes in the Real World: The Elusive Nature of Glycemic Control, 2017

Poor Medication Adherence in T2DM Remains Key Issue for Millions of Americans Despite Availability of Weekly GLP-1s



Adapted from Mody, 2018

Despite Weekly GLP-1s, Large Treatment Persistence Gaps Exist Every 6 Months; New Twice-Yearly Dosing Options May Help



Adapted from Mody, 2022

Data Support Positive Benefit-Risk for ITCA 650 With Class-Labeled AKI Warning and Post Approval CVOT

✓ Extended Maintenance Therapy Option Needed

- Uncontrolled HbA_{1c} is a crisis in > 50% patients
- Often caused by non-adherence and non-persistence to injections
- New extended maintenance dosing options are needed

✓ Unequivocal Sustained Efficacy with 6-Month Dosing

- 4 successful Phase 3 trials
  - > 5,800 T2DM patients
  - > 22,000 implants
- Consistent and highly effective exenatide delivery
  - Improved HbA1c
  - Improved weight loss
- Twice-yearly dosing
- Clinical data validated IVR limit specifications as effective and safe for intended / labeled use

✓ Safety In-Line with GLP-1s, and Label

- GI AEs rates in-line with class, majority at dose initiation and escalation
- GI AEs and AKIs GLP-1 class effects seen in post-marketing reports, and more RCT AKI Imbalances
- GLP-1s carry Warnings and Risk Mitigation for AKI
- Met FDA's pre-approval CVOT requirements

Agenda

Clinical Efficacy	**Daniel Drucker, MD, FRS, FRCPC, OC** Senior Scientist, Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital, Professor of Medicine, University of Toronto
Clinical Safety	
CDER's Prioritized Issues 1) AKI 2) MACE 3) Clinical validation of Device IVR	**Dr. Daniel Drucker** **Philip Sager, MD, FACC, FAHA, FHRS** Adjunct Professor, Stanford University School of Medicine Member, Executive Committee, Cardiac Safety Research Consortium
Benefit / Risk & Conclusions	**Kurt Graves** Chairman, President & CEO

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***Former Subject Matters Experts At Intarcia**

Clinical Development Program and Efficacy Outcomes

Unequivocal efficacy established in 4 Phase 3 studies

Daniel Drucker, MD, FRS, FRCPC, OC

Senior Scientist at the Lunenfeld-Tanenbaum Research Institute, Mount Sinai Hospital,

University Professor, University of Toronto

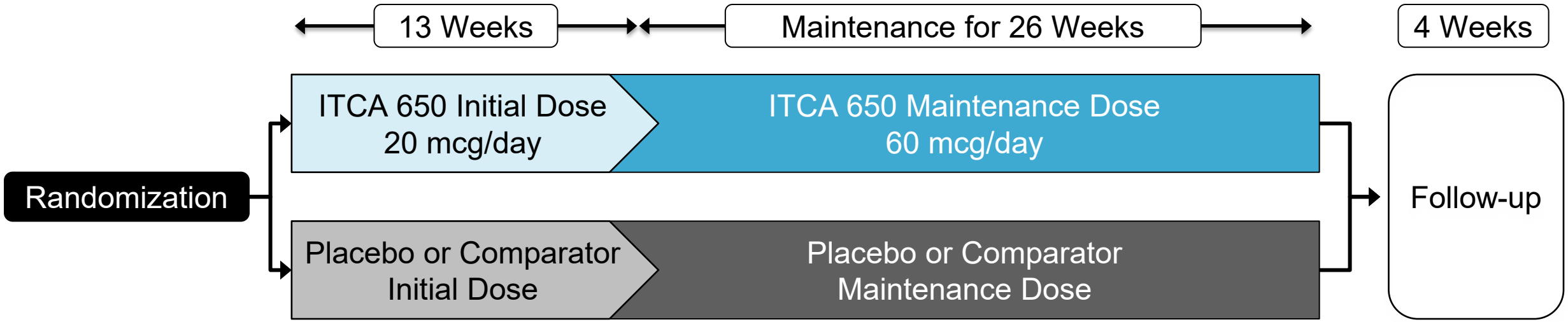
ITCA 650 Use in Patients with T2DM Supported by 4 Successful, Well-Conducted Clinical Studies

Study 103[a]	Study 103 HBL[b]	Study 105[c]	Study 107 (CVOT)[d]	Study 201
Randomized, placebo-controlled, dose confirmation*	Open-label, single arm	Randomized, controlled comparison to sitagliptin 100 mg/day	Pre-submission, randomized, placebo-controlled, CV outcomes trial	Open-label, randomized safety trial of switch from liraglutide
T2DM with baseline HbA_{1c} >7.5% to <10%	T2DM with baseline HbA_{1c} >10% to ≤12	T2DM with baseline HbA_{1c} >7.5% to ≤10.5%	T2DM with baseline HbA_{1c} >7.5% to <10%	T2DM with baseline HbA_{1c} >7.5% to <10%
N=460 (US only)	N=60	N=535	N=4,156	N=136

*Tested maintenance doses of 40 and 60 mcg/day

a. Rosenstock, ADA Meeting (2015); b. Henry, ADA Meeting (2015); c. Rosenstock, ADA Meeting (2016); d. Ruff et al (2022)

Randomized Controlled Studies Followed Traditional T2DM Design as Adjunct to Diet and Exercise



Studies Used Well-Accepted T2DM Endpoints

Studies 103 and 105

Primary Endpoint

- Change from baseline in HbA_{1c}

Key Secondary Endpoints

- Change from baseline in body weight
- % with HbA_{1c} < 7%

Other Secondary Endpoints

- % with HbA_{1c} decrease > 0.5% and weight loss

Study 107 (Pre-approval CVOT)

Primary Endpoint

- Time to MACE+
  - CV death, non-fatal MI, non-fatal stroke, hospitalization for unstable angina

Efficacy Endpoints

- Change from baseline in HbA_{1c}
- Change from baseline in body weight
- % with HbA_{1c} < 7%

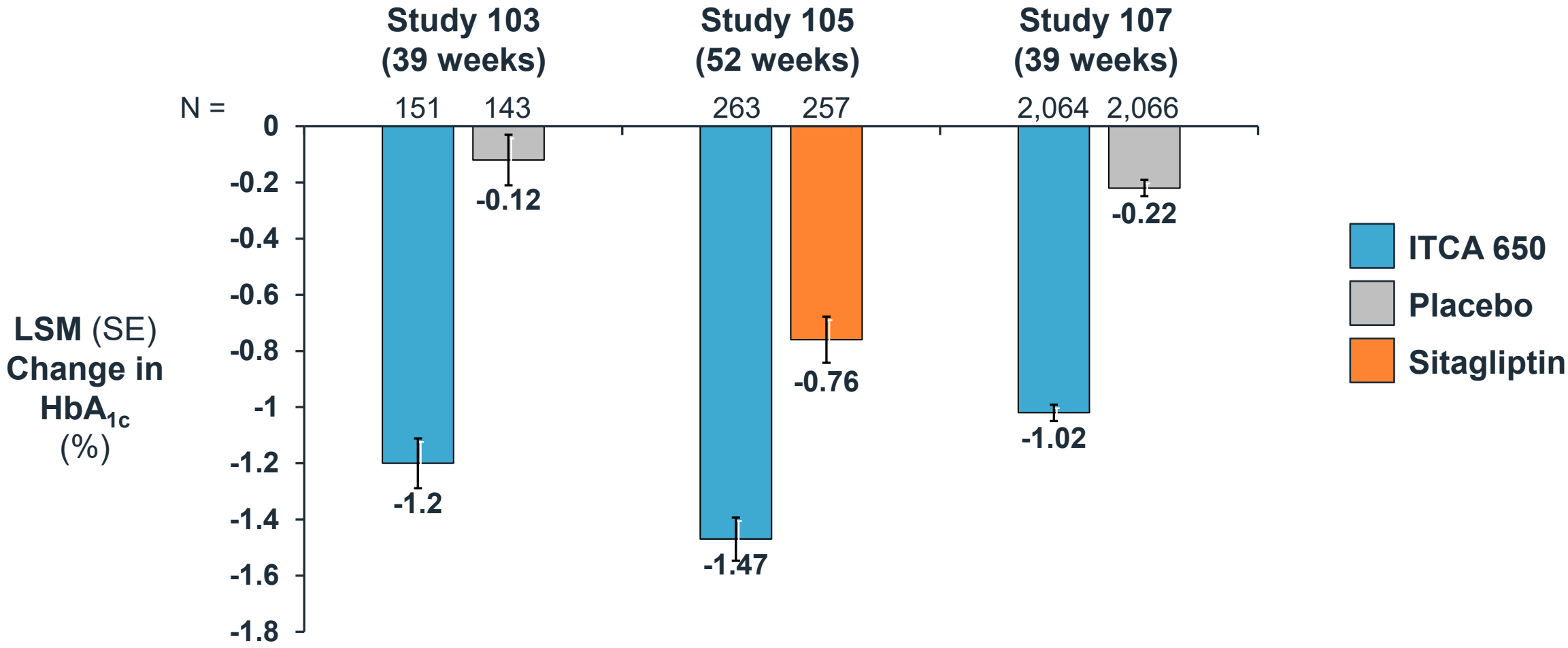
ITCA 650: Unequivocal Efficacy Demonstrated and Sustained in all Randomized, Controlled Studies

	Study 103 (vs Placebo) N = 151	Study 105 (vs Sitagliptin) N = 263	Study 107 (CVOT) (vs Placebo) N = 2,064
Met primary endpoint	✓[1]	✓[1]	✓[2]
Key Efficacy Endpoints	39 Weeks	52 Weeks	39 Weeks
Change from baseline in HbA_{1c} (p-value vs comparator)	< 0.001	< 0.001	< 0.001*
Change from baseline in weight (p-value vs comparator)	< 0.001	< 0.001	< 0.001*

- Similar efficacy to published results from other exenatide products

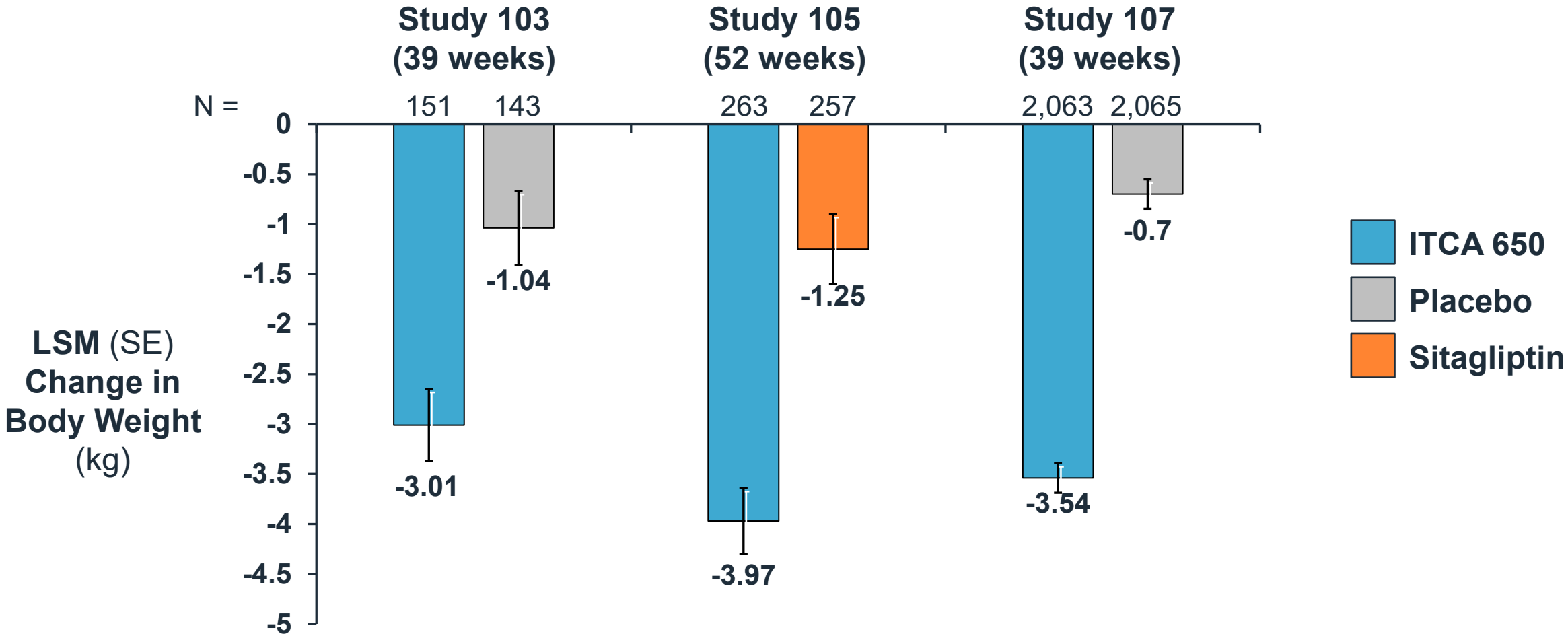
1. Change from baseline in HbA_{1c}; 2. Time-to-MACE HR upper 95% CI bound < 1.8; * nominal p-value

ITCA 650 Change from Baseline HbA_{1c} at Week 39 and Week 52 (mITT Population)



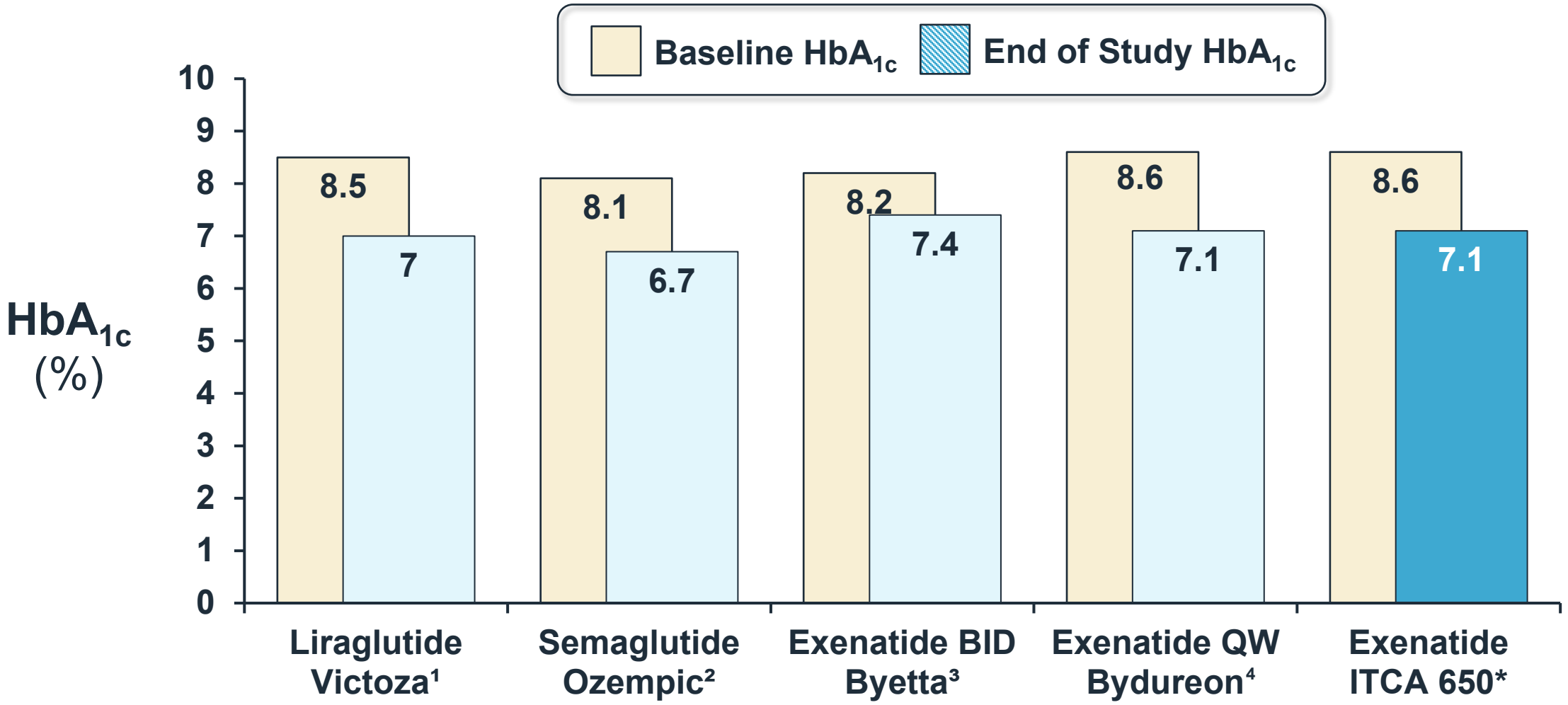
1. Rosenstock J et al. ADA Annual Meeting; June 5-9, 2015; Boston, MA. Abstract 276-OR;
2. Rosenstock JR. Abstract Presented at 2016 ADA Scientific Sessions, June 10-14, 2016, New Orleans, LA 183-OR

Studies 103 / 105 / 107: ITCA 650 Change from Baseline Weight (mITT Population)



1. Rosenstock J et al. ADA Annual Meeting; June 5-9, 2015; Boston, MA. Abstract 276-OR;
2. Rosenstock JR. Abstract Presented at 2016 ADA Scientific Sessions, June 10-14, 2016, New Orleans, LA 183-OR

ITCA 650 Implants Delivering Exenatide Provide Efficacy In-Line with Exenatide and Approved GLP-1s



1. Pratley, Lancet 2010; 2. Ozempic label, FDA.gov; 3. Defronzo, Diabetes Care 2005; 4. Duration 2 – Bergenstal, Lancet 2010; *NDA: Study 105

ITCA 650 Safety

Aligns with Well-Established Profile of Exenatide & Approved GLP-1s with AKI Labels

All approved GLP-1 products include class labeled Warnings and Precautions for AKI

Pooled Safety Across Studies 103, 105, 107 Aligns with Established Safety of Exenatide

Preferred Term	Pooled ITCA 650 20 / 60 mcg/day N = 2,488	Pooled Placebo N = 2,228
Any AE	**74%**	**64%**
Severe AE	**12%**	**10%**
SAEs	**14%**	**14%**
AEs leading to discontinuation of study medication	**12%**	**5%**
AEs leading to death	**2%**	**2%**

On-Treatment / Treatment-Emergent AEs (Protocol):

- **Treatment-emergent AEs (TEAEs) were reported following the start of the procedure for the initial placement of an ITCA 650 or ITCA placebo up to and including the final removal of an ITCA 650 or ITCA placebo.**
- **All post-treatment AEs reported after the date of study medication stop and through the follow-up visit (EOT + 4 weeks).**

Most Common AEs (> 5%) Gastrointestinal in Nature, and Aligns with GLP-1s / Labeling

Preferred Term	Pooled ITCA 650 20 / 60 mcg/day N = 2,488	Pooled Placebo N = 2,228
Any AE	**57%**	**42%**
Nausea	**22%**	**4%**
Vomiting	**15%**	**1%**
Hypoglycemia	**9%**	**4%**
Diarrhea	**8%**	**4%**
Urinary tract infection	**6%**	**5%**

Pooled Safety includes Studies 103, 105, 107
No clinically relevant (major) hypoglycemia reported when ITCA 650 used without sulfonylureas or insulin. Incidence of major hypoglycemia was 0.3% in ITCA 650-treated patients only when ITCA 650 used in combination with sulfonylureas or insulin.
ITCA 650 and GLP-1s generally not associated with risk of hypoglycemia when used without insulin or SUs.

GLP-1 GI AEs are a Class Effect and Risk Factor Linked to Serious AKI Events, as Noted in Warnings

- Hypovolemia: common cause of AKI from dehydration or significant bleeding
  - Occurs with transient GLP-1 GI AEs when initiating or escalating doses
  - More common in higher risk patients with pre-existing renal impairment
  - Added dehydration/renal risks: metformin[1], diuretics, ARBs/ACEs, NSAIDS

FDA AKI Warnings Focus on Link with GI AEs:

"Monitor renal function when **initiating** or **escalating** doses of [GLP-1] in patients reporting severe adverse **GI reactions**."

1. Bettge, 2017; Metformin labeling

Incidence of ITCA 650 GI AEs and GI AE Discontinuation Rates is In-Line with Approved GLP-1s

	GI AEs (Mostly Nausea, Vomiting, Diarrhea)	Discontinuation Rates Due to GI AEs
Exenatide (ITCA 650)* 20/60 mcg/d	37%	8%
Exenatide (BID - Byetta) 20 mcg/d	44%	14%
Exenatide (QW - Bydureon)* 2 mg/wk	27%	5%
Liraglutide 1.8 mg*	41%	5%
Liraglutide 3.0 mg	68%	6%
Semaglutide 0.5 mg*	51%	6%
Semaglutide 1 mg*	52%	10%
Semaglutide 14 mg (oral)	41%	8%
Semaglutide 2.4 mg	73%	5%

Treatment Emergent GI AE data; FDA medical reviews/labeling; *CVOT GI AE data where AKI SAE imbalances exist for ITCA 650, Semaglutide and Liraglutide

GLP-1 AKI Post Marketing Reports Led to Initial AKI Warnings; Wegovy's AKI Warning Notes "AKI Occurred in Clinical Trials"[1]

FDA's FAERS Database – Thousands Of GLP-1 AKI SAEs[2]

FDA Adverse Events Reporting System (FAERS) Public Dashboard

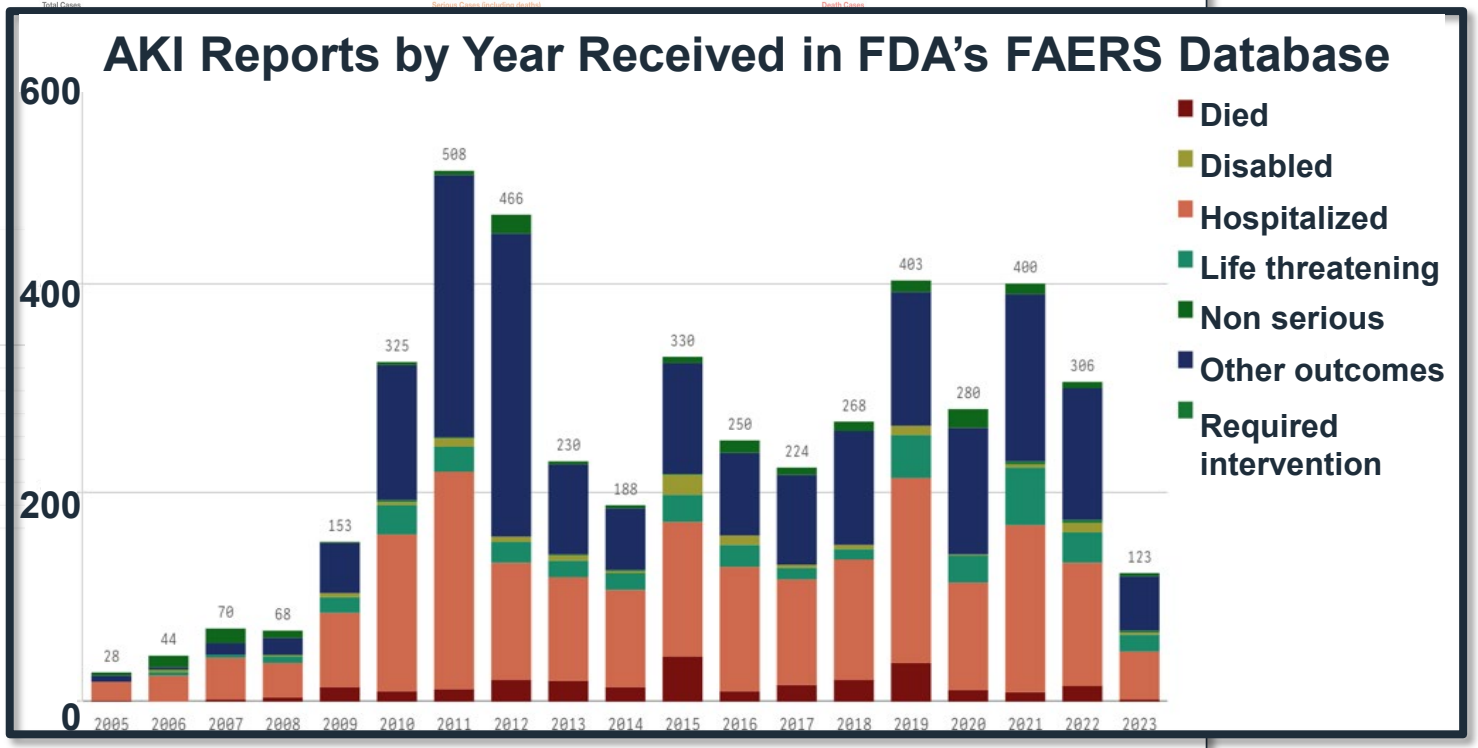
Home | Demographics | Reaction Group | Reaction | Listing of Cases | Disclaimer | Report a Problem | FAQ | Site Feedback | Search by Product

DULAGLUTIDE (G); EXENATIDE (G); LIRAGLUTIDE (G); SEMAGLUTIDE (G); WEGOVY (P)

	3,221
Number of Cases	**3,221**
Acute Kidney Injury	1,534
Renal Failure	1,210
Renal Impairment	426
Renal Injury	104
Anuria	45
Prerenal Failure	11

FAERS events are known to be significantly under-reported

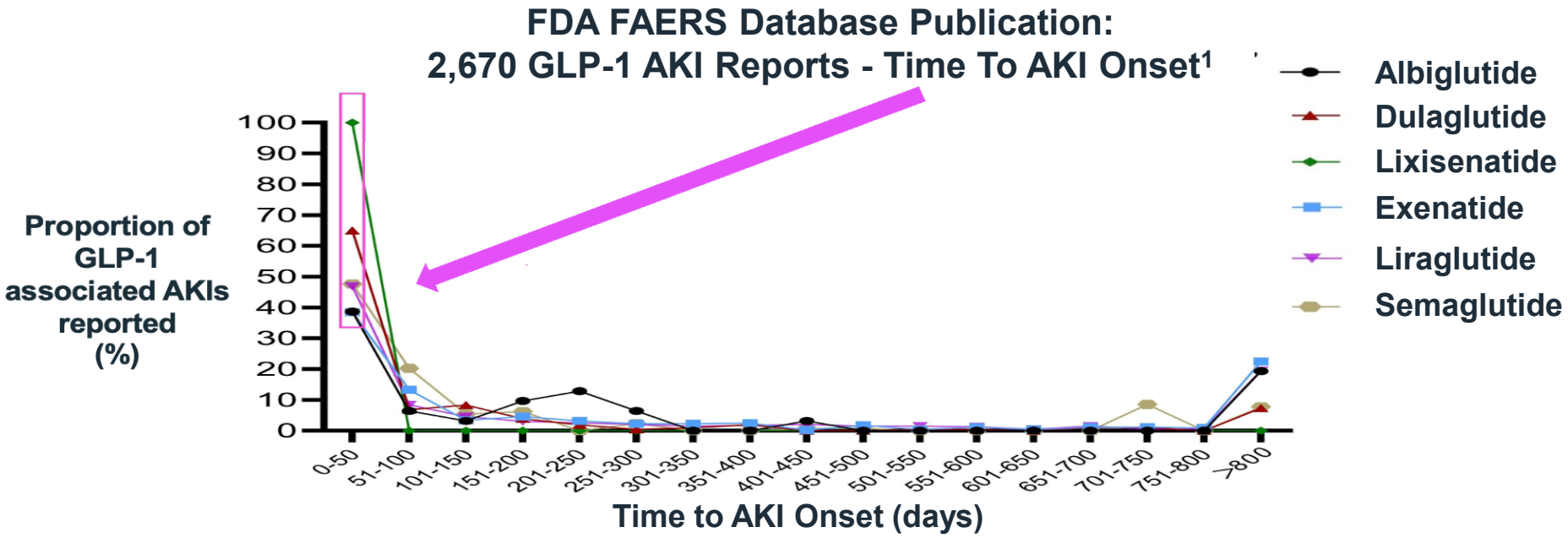
Data as of March 31, 2023



Vulnerability Disclosure Policy

1. **Wegovy (semaglutide) AKI Warning: "Acute kidney injury occurred in clinical trials** in 7 adult patients (0.4 cases per 100 patient years) receiving WEGOVY® versus 4 patients (0.2 cases per 100 patient years of exposure) receiving placebo. **Some of these adverse reactions occurred in association with gastrointestinal adverse reactions or dehydration**.
2. **SAE cases reported on FAERS typically only represent a small % of actual cases**

FAERS Publication Shows Majority of GLP-1 AKIs Occur Quite Early on Low Initial Doses; FDA Warnings Emphasize Majority* Had GI AEs[1]



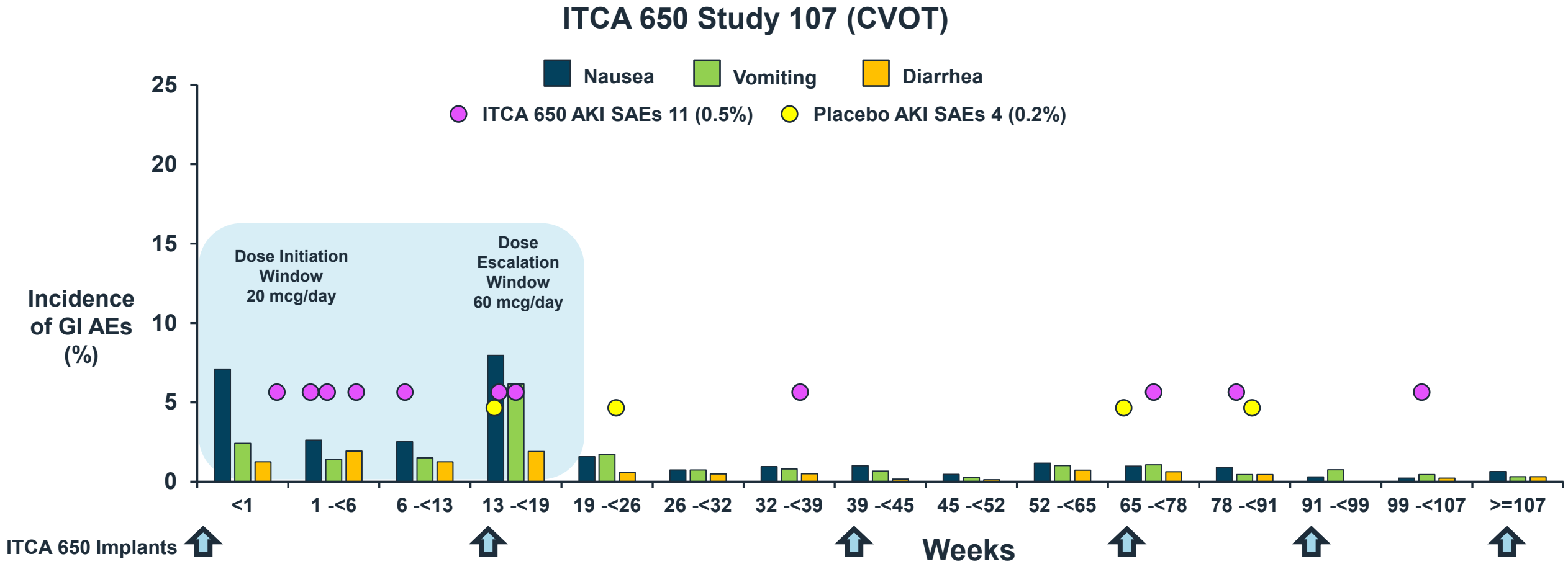
GLP-1 AKI WARNINGS

"**A majority** of reported [AKIs] occurred in **patients who experienced nausea, vomiting, or diarrhea**, leading to volume depletion"

"Monitor **renal function** when **initiating** or **escalating** doses of [GLP-1] in patients reporting severe adverse **GI reactions**."

1. Frontier. Endocrinol., 13 December 2022 – FAERS

Transient GI AEs at Dose Initiation/Escalation Likely Contributed To Early Numeric AKI Imbalance; AKI Balanced Out After GI AEs Drop



*ITCA 650 AKI SAEs had risk factors in each case: 1) Pre-existing renal impairment and 2) use of concomitant medicines known to increase risk of dehydration and AKI (diuretics, metformin, ARBs/ACEs, NSAIDS)

Transient GLP-1 GI AEs Leading to Dehydration Represent Mitigatable Risk for AKI

- AKI risk can be monitored and mitigated with warnings and proactive prevention[1]
  - Inform patients about early GI AEs and risk of AKI if dehydration occurs, stay hydrated
  - Modify / stop suspected medications contributing to dehydration (incl. ITCA 650), give fluids
  - Monitor renal function in renal impaired during early dosing windows with transient GI AEs
  - ITCA 650 will be administered in trained / certified offices where education and risk mitigation measures implemented; additional medical staff and online training and videos support 24/7

1. Wharton 2022.

AKI Safety for ITCA 650 and GLP-1 Class

ITCA 650 NDA: There Are 14 Total AKI SAEs On Drug & 4 On Placebo - On Treatment AKI SAE Imbalance In Trial 107 (CVOT) Is 11 vs 4

	ITCA 650	Placebo
Study 107	N = 2,075	N = 2,081
On Treatment Serious AKI	**11 (0.5%)**	**4 (0.2%)**
AKI SAE leading to death	0	2
Non Treatment Emergent Serious AKI	**2**	**0**
Study 105	N = 263	N = 257
On Treatment Serious AKI	**1***	**0**

*** Due to major bleed not drug related; p.44**

CDER BD **incorrectly** asserts there were 2 other AKI cases ***"experienced AKI and GI side affects at time of death"*** in study 107
Events leading to deaths did not involve proximal GI AEs, patients died of other causes not drug related; Case narrative facts p.39

CDER's Briefing Erred In Asserting That 2 AKIs In Study 107 Involved Patients "Experiencing AKI and GI Symptoms When They Died" [1,2]

Sex / Age	2 Known AKI Risk Factors: Baseline Renal Stage	2 Known AKI Risk Factors: Concomitant Medications	Days on Therapy at Onset	GI AEs	Creatinine at event (KDIGO Grade)	Patient Recovered
M / 68	Mild (eGFR: 88 mL/min)	Diuretics, ACE, NSAID	**649** **747**	(Day 642) Yes due to viral gastroenteritis that resolved (Day 747) **No Proximal GI AEs. Significant GI bleed proximal to AKI**	NR	Resolved (Day 652) No; Died on Day 755 due to **Multi-organ Dysfunction Syndrome** (Not study drug related)
M / 66	Moderate (eGFR: 54 mL/min)	Metformin, ACE-I / HCTZ	**110**	**No Proximal GI AEs**	NR	No; Died of **Acute Coronary Event** (Not study drug related)

1. CDER BD (p.10) for the first time asserts 2 subjects **"were experiencing AKI and GI symptoms at the time of their deaths". Case narrative facts in NDA don't support.**
2. CDER BD adds: "CDER therefore considers the actual imbalance in serious AKI events to be 16 subjects (0.64%) versus 4 subjects (0.16%)" and assert a >3x risk. **Not so.**

Case Report Facts Do Not Support CDER's Assertion that 2 Non-Serious AKI Patients were "Experiencing AKI and GI Symptoms When They Died"

Sex / Age	Sequence of Events Leading to Death Were Not Study Drug Related
M / 68	• **Day 642:** Diagnosed non-serious viral gastroenteritis causing dehydration, malaise, and associated GI AEs. • **Day 649** Admitted for chest pain, developed **non-serious case of AKI same day** (no labs) **that resolved on Day 652.** • Case record: "investigator confirmed symptoms of dehydration, malaise, and GI AEs were from viral gastroenteritis" **100 Days Later** • **Day 747:** Presented at outlying facility for 2–3 days of chest pain. Admitted with **diagnosis of (NSTEMI). An AKI was also diagnosed, no GI AEs were noted**. Subject was transferred to a hospital same day for additional labs and endoscopy. • **Day 747:** Upon admission, patient had **hematemesis** (vomiting of blood) and labs and endoscopy showed **significant ongoing GI bleed (hemoglobin 7.2g/dl) and associated acute renal failure requiring dialysis (eGFR 13, creatinine 4.3 mg/dl).** The subjects condition started to decline later the same day with hypotension, worsening respiratory failure/ARDS, and subsequently developed into progressive multi-organ dysfunction. • **Day 755:** Patient died. **Cause of Death: Multi-organ dysfunction syndrome.** Not study drug; **No Proximal GI AEs.**
M / 66	• **Day 110: Non-serious** AKI **related to worsening CKD.** Creatinine was 1.61 vs 1.33 four months earlier. Patient instructed to stop metformin. **There were no GI AEs reported.** • **Day 119: Patient died.** Family was with subject at home in morning and later found him deceased. • **Cause of Death: Acute coronary event.** Not study drug related; **No Serious AKI Occured, No Proximal GI AEs.**

Study 107 (CVOT): AKI Events Occurred in Patients with GI AEs at Dose Initiation and Escalation Enabling Risk Mitigation with Clear Warnings

Sex / Age	2 Known AKI Risk Factors: Baseline Renal Impairment	2 Known AKI Risk Factors: Concomitant Medications	Days on Therapy at Onset	GI AEs	Creatinine at event (KDIGO Grade)	Patient Recovered
M / 76	Mild (eGFR: 63 mL/min)	Metformin, diuretic, ARB	Day 7	Mild/Mod Nausea Diarrhea	Grade 3	**Yes**
M / 62	Mild (eGFR: 87 mL/min)	Metformin, 3 diuretics, ACE-I	Day 8	Mild Nausea Vomiting	Grade 3	**Yes**
M / 73	Mild (eGFR: 62 mL/min)	Metformin	Day 8	Mod Nausea Vomiting Diarrhea	Grade 2	**Yes**
M / 67	Mild (eGFR: 68 mL/min)	Metformin, NSAID, ACE-I	Day 19	Mod Vomiting	Grade 3	**Yes**
F / 68	Moderate (eGFR: 57 mL/min)	Metformin, diuretics, ACE-I	Day 75	Mod Nausea Vomiting Diarrhea	Grade 1	**Yes**
M / 43	Moderate (eGFR: 48 mL/min)	Metformin, ARB	Day 111	Mild/Mod Vomiting	Grade 1	**Yes**

KDIGO Staging: Grade 0: Serum creatinine <1.5 times baseline; Grade 1: Serum creatinine 1.5–1.9 times baseline; Grade 2: Serum creatinine 2.0–2.9 times baseline; Grade 3: Serum creatinine ≥ 3.0 times baseline.

Study 107 (CVOT): Remainder of 11 AKI SAE Events; Not All Were Study Drug Related (e.g. Case with Major Bleed and no GI AEs)

Sex / Age	2 Known AKI Risk Factors: Baseline Renal Impairment	2 Known AKI Risk Factors: Concomitant Medications	Days on Therapy at Onset	GI AEs	Creatinine at event (KDIGO Grade)	Patient Recovered
M / 74	Mild (eGFR: 62 mL/min)	Metformin, diuretics, ACE-I	Day 117	Severe Diarrhea	Grade 2	**Yes**
F / 75	Mild (eGFR: 64 mL/min)	Metformin, NSAIDs, ARB, Antibiotics	Day 281	Mild Vomiting	Grade 3	**Yes**
F / 66	Moderate (eGFR: 58 mL/min)	Metformin, ARB	Day 500	No GI AEs Major Bleed	Grade 2	**Yes**
F / 64	Mild (eGFR: 83 mL/min)	Metformin	Day 559	Mod Vomiting Diarrhea	Grade 3	**Yes**
M / 73	Moderate (eGFR: 50 mL/min)	Metformin, NSAID, Antibiotic	Day 748	Mod/Severe Nausea Vomiting	NA	**Yes**

KDIGO Staging: Grade 0: Serum creatinine <1.5 times baseline; Grade 1: Serum creatinine 1.5–1.9 times baseline; Grade 2: Serum creatinine 2.0–2.9 times baseline; Grade 3: Serum creatinine ≥3.0 times baseline.

Study 107 (CVOT): CDER's Number of 14 On-Treatment AKI SAEs is Inflated by 2 Non-Treatment Emergent* Cases; Also No GI AEs

Sex / Age	2 Known AKI Risk Factors: Baseline Renal Stage	2 Known AKI Risk Factors: Concomitant Medications	Days on Therapy at Onset	GI AEs	Creatinine at event (KDIGO Grade)	Patient Recovered
M / 63	Moderate (eGFR: 52 mL/min)	Multiple Diuretics, ARB, NSAID	Day 1 **(AKI prior to First implant)**	**None**	Grade 1	**Yes; Completed Trial**

Medical History

Over 21 days prior to starting therapy patient had **worsening to moderate renal impairment and creatinine increases from 1.17 mg/dL to 1.38 mg/dL just prior to the initial insertion** of ITCA 650 which is when treatment emergent period begins. Patients worsening CKD and use of multiple con-meds known to contribute to AKI is most plausible cause of event prior to therapy. **No proximal GI AEs were involved.**

M / 65	Mild (eGFR: 80 mL/min)	Diuretics ACE-I	**Day 312 (44 days / 6 weeks after treatment stopped)**	**None**	None	**Yes**

Medical History

* Treatment emergent period defined starting at/after treatment initiation and ending at last device removal. End of treatment (EOT) AE window was 4 weeks after final device removal. **This event occurred > 6 weeks after final removal** of ITCA 650. **Also no GI AEs**

KDIGO Staging: Grade 0: Serum creatinine <1.5 times baseline; Grade 1: Serum creatinine 1.5–1.9 times baseline; Grade 2: Serum creatinine 2.0–2.9 times baseline; Grade 3: Serum creatinine ≥3.0 times baseline.

Study 105: CDER's BD Shows Comparative AKI SAE Numbers Using This Single Case Where AKI Was Associated With A Major Bleed

Sex / Age	2 Known AKI Risk Factors: Baseline Renal Stage	2 Known AKI Risk Factors: Concomitant Medications	Days on Therapy at Onset	GI AEs	Creatinine at event (KDIGO Grade)	AKI Resolved
M / **53**	Mild (eGFR: 79 mL/min)	Metformin, ACE-I, Diuretic, NSAID, Cephalexin	Day 55	Gastroenteritis related nausea vomiting	NR	**Yes, after major bleed was managed (not study drug related)** Completed 12-month study

Medical History

- **Patient had illness earlier in same month**. Bacterial infection, gastroenteritis (investigator noted fever, belly pain, **nausea, vomiting was due to gastroenteritis**). Patient treated with cephalexin + multiple con-meds.
- **Patient hospitalized with a significant and ongoing bleed proximal to the AKI SAE (Hemoglobin of 7.4 g/dL vs 12 g/dL reported earlier in same month). SCr levels during the bleed in the hospital were 4.9 mg/dl vs 1.0 mg/dl a month earlier. Patient recovered from the major bleed and AKI. Finished the trial on ITCA 650.**

CDER's briefing document adds this single case (a major bleed/not drug related) to the total AKI SAE cases when they assert risk calculations and comparative graphs/plots vs. other GLP-1s. Adding this case and/or adding the 2 not "on-treatment" / non-treatment emergent AKI SAEs in Study 107 erroneous inflates cases

Addressing CDER's Core AKI Assertion vs Other GLP-1s

"The numeric imbalance in AKI SAEs in Study 107 suggests ITCA 650 causes AKI to a greater extent than other GLP-1s which did not show numeric imbalances in large randomized [CVOT] trials."[1]

1. CDER's Proposed Order To Deny ITCA 650 @ p.44

Intarcia Addressed this Concern Using Standardized Serious AKI Assessment Methods for GLP-1 RCTs with Public Data

- Used standard randomized data from large CVOTs: drug vs placebo
- Used on treatment standard AKI search terms (MedDRA narrow scope)
- Used standard total serious AKI events; key to include repeat AKI SAEs[1,2]

Patients with renal impairment (the majority in CVOTs) who have repeat AKI SAEs and hospitalizations have a 14-fold increased risk of reaching ESRD and renal replacement therapy (RRT)[1,2]

1. Influence of multiple episodes of AKI on survival and accelerated progression to end stage kidney disease in patients with renal impairment: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0219828; 2. CDER FDRR letter 7/30/2020: "the overall clinical impact of two events [i.e. repeat AKI SAEs] in a single subject is probably less than the overall impact of two subjects, each with one event"

Published Data Show Numeric Imbalances In Both Serious and Non-Serious AKIs In All 3 GLP-1 CVOTs; Not Isolated To ITCA 650

Unfavorable Numeric Imbalances In Both Serious & Non-Serious AKIs (On Treatment)

GLP-1 CVOTs	(Serious AKI + Non-Serious)	Serious AKI Alone
	Drug vs Placebo	Drug vs Placebo
ITCA 650 CVOT[1] N=2075	1.9% vs 1.2%	0.5% vs 0.2%
Semaglutide SUSTAIN-6 CVOT[2] N=826 0.5mg Dosing Arm	5.1% vs 4.1%	3.1% vs 2.2%
Liraglutide LEADER CVOT[3] * N=4668	4.8%* vs 4.5%	3.0%* vs 2.9%

* AKIs above for liraglutide don't include "repeat" AKI SAEs (23 on liraglutide) where renal impaired patients have a 14-fold increased risk of ESRD & RRT. See P. 49

1. ITCA 650 NDA; AKI Expert Report in NDA and CSR Study 107
2. Semaglutide SUSTAIN-6 Randomized AKIs on 0.5mg drug vs. 0.5mg volume-matched placebo control, NEJM, 2016; serious AKI imbalance on ClinicalTrials.gov
3. Liraglutide EMDAC Materials: Sponsor Reported Serious and Non-Serious AKI Events In LEADER EMDAC Materials (p.75)

LEADER CVOT: Sponsor's Liraglutide EMDAC*Data Shows Imbalances in AKI SAEs, Repeat AKIs, Non-Serious AKIs, Deaths

Table 19 pg 75 of Novo Nordisk EMDAC BD	Liraglutide (LEADER CVOT) N = 4,668			Placebo (LEADER CVOT) N = 4,672		
	N	%	Events	N	%	Events
Acute Renal Failure (AKI)	156	3.3	179	152	3.3	171
AKI Serious*	141	3.0	164	136	2.9	153
AKI SAE/Renal Deaths**			11			5

* MedDRA AKI Narrow Scope Search Terms; E = Total AKI SAE events Reported
* Novo Nordisk FDA EMDAC Briefing Materials, p. 75, AKI Table 19, 2017; ** FDA's LEADER EMDAC Briefing Notes 11 vs 5 Adjudicated Deaths & Slide 35
* 23 of the 164 total AKI SAEs were repeat AKI SAEs in renal impaired patients that have a 14-fold increased risk of ESRD and renal replacement therapy

LEADER CVOT: Liraglutide Total AKI SAEs Were Imbalanced[1], Particularly In Normal & Mild Renal Impairment at Baseline

AKI SAEs By Renal Function – Per Standard MedDRA Search Terms[1,2]

	Normal Renal Function		Mild Impairment		Moderate Impairment		Severe Impairment	
	Lira N=1,620	**Placebo** N=1,655	**Lira** N=1,932	**Placebo** N=1,975	**Lira** N=999	**Placebo** N=935	**Lira** N=405	**Placebo** N=366
Total AKI SAEs[1,2]	20 **(1.2%)**	12 **(0.7%)**	51 **(2.6%)**	40 **(2.0%)**	69 **(6.9%)**	79 **(8.4%)**	18 **(4.4%)**	21 **(5.7%)**
Acute kidney injury[1]	16 (1.0%)	10 (0.6%)	36 (1.9%)	31 (1.5%)	49 (4.9%)	49 (5.2%)	10 (2.5%)	9 (2.4%)
Renal impairment[1]	2 (0.1%)	1 (<0.1%)	7 (0.4%)	2 (0.1%)	6 (0.6%)	8 (0.8%)	5 (1.2%)	4 (1.1%)
Renal failure[1]	2 (0.1%)	1 (<0.1%)	6 (0.3%)	7 (0.4%)	14 (1.4%)	22 (2.4%)	3 (0.7%)	8 (2.2%)

1. Sponsors AKI SAE disclosures to EMDAC show a total of 164 AKI SAEs on drug vs. 153 on placebo (prior slide);
2. FDA's LEADER EMDAC Briefing Materials – Table 57 - Proteinuria events removed as not a MedDRA AKI SAE search term; nor is proteinuria used in other GLP-1 comparisons by CDER

SUSTAIN-6 CVOT: Semaglutide Also Has A Serious AKI SAE Numeric Imbalance* Not Favoring The Approved 0.5mg Dose

SUSTAIN-6 CVOT* 4 Arm Trial ARF SAEs	Sema 0.5 mg N = 826	Total AKI SAE Events	Placebo 0.5 mg N = 824	Total AKI SAE Events	Sema 1.0 mg N = 822	Total AKI SAE Events	Placebo 1.0 mg N = 825	Total AKI SAE Events
ARF SAEs Total	26 (3.1%)	30[1]	18 (2.2%)	18	10 (1.2%)	12	24 (2.9%)	26

[1]FDA's NDA Medical Review Notes 3 of the 30 AKI SAEs Above on Semaglutide 0.5mg Dose Resulted In Deaths
FDA's NDA Review Also Noted 3 Addition AKI SAEs in Other NDA Trials In The NDA & Noted All 3 Had GI AEs Dehydration

Standard MedDRA Narrow Scope AKI Search Terms

*Source: Not In Any EMDAC Materials; The Source Of This AKI SAE Data (By Dose/Not Pooled) Is The Sponsor's Own ClinicalTrials.gov AKI SAEs Listings Months After Approval

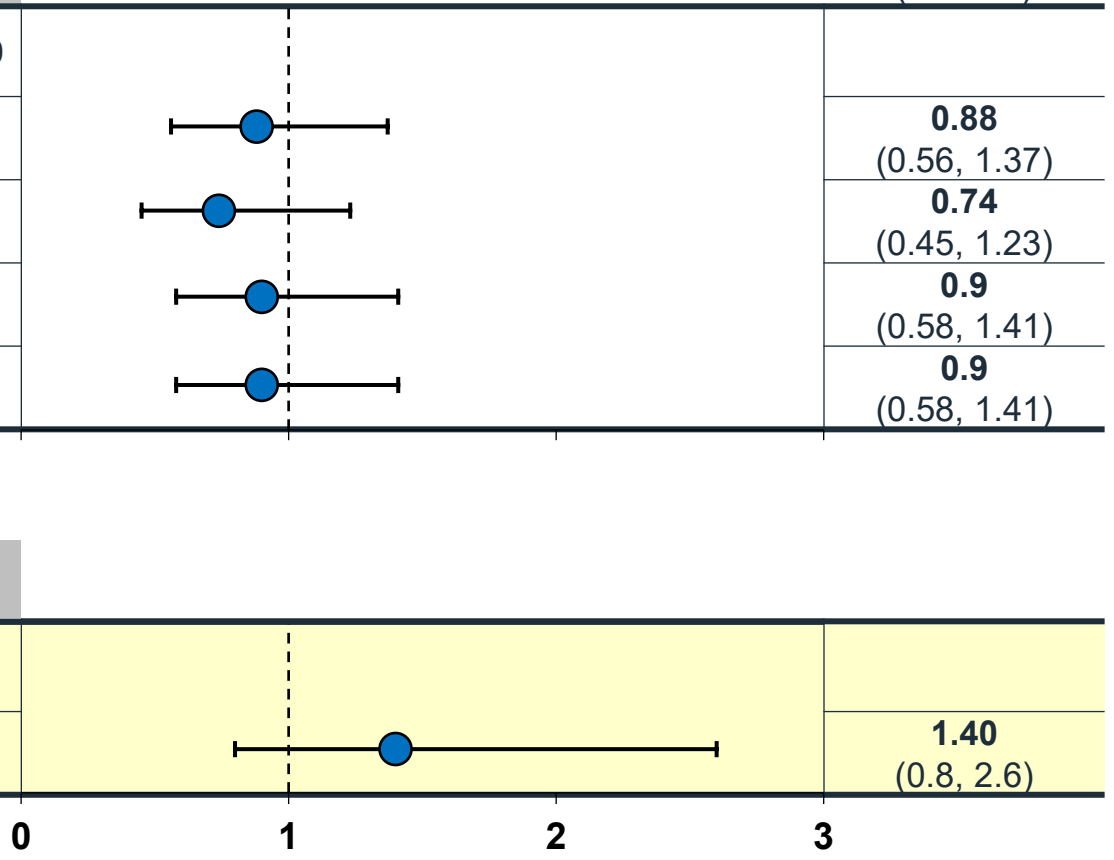
SUSTAIN-6 CVOT: AKI SAEs Were Pooled In CDER's Plots (Top) Which Omitted A Pre-Specified AKI SAE Imbalance* (Bottom)

FDA SUSTAIN-6 AKI SAE GRAPHS USED POST-HOC POOLING OF AKI SAEs
Omits Pre-Specified 0.5mg vs. 0.5mg placebo

	Sema	Placebo	Risk Ratio (95% CI)
SUSTAIN-6	**N = 1648**	**N = 1649**	
AKI FDA Broad Scope Non-serious	36	41	**0.88** (0.56, 1.37)
AKI FDA Narrow Scope Non-serious	26	55	**0.74** (0.45, 1.23)
AKI FDA Broad Scope Serious	37	41	**0.9** (0.58, 1.41)
AKI FDA Narrow Scope Serious	36	40	**0.9** (0.58, 1.41)

SPONSORS PROTOCOL PRE-SPECIFIED AKI AS AN ENDPOINT & TWO DOSES NOT TO BE POOLED **

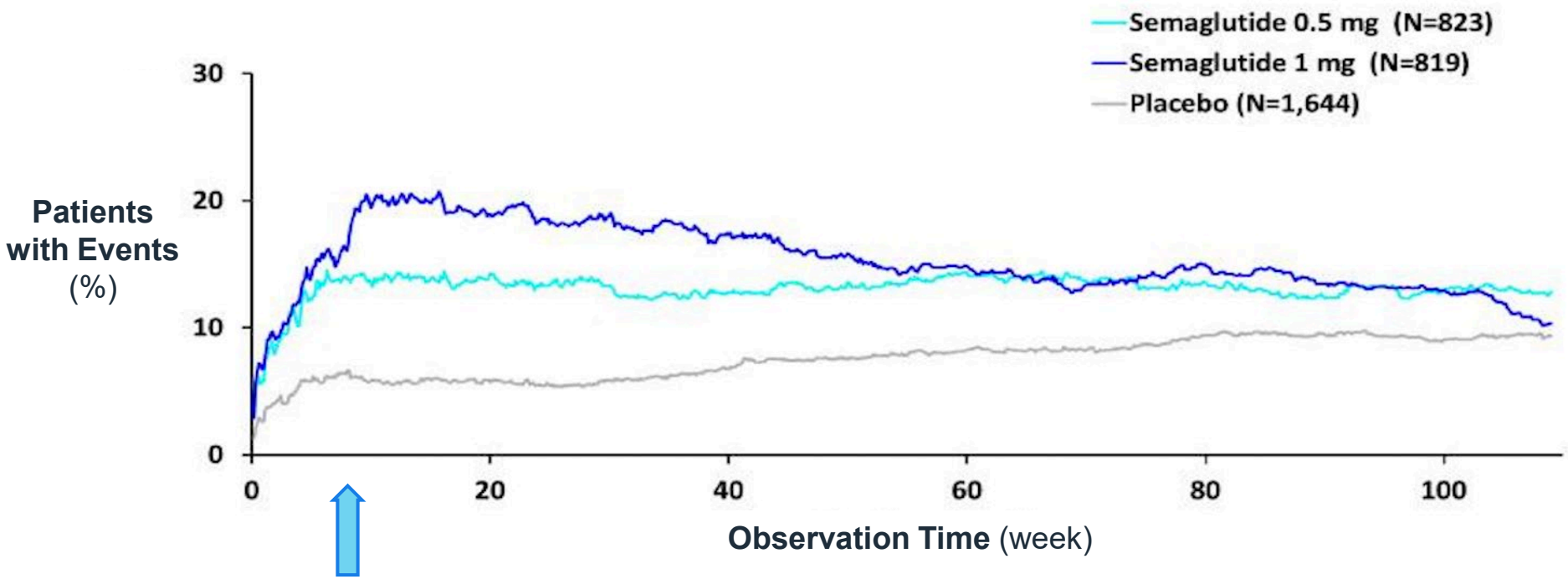
	Sema	Placebo	
SUSTAIN-6 (0.5 mg arm)	**N = 826**	**N = 824**	
AKI SAE's	26	18	**1.40** (0.8, 2.6)



** CDER's briefing document outlines numerous cross-trial AKI comparison tables, plots and graphs that all use 'post-hoc' pooling to omit the 0.5mg imbalance
*Sponsor's SUSTAIN-6 Clinicaltrials.gov AKI SAEs 2018; Standard MedDRA AKI SAE Narrow Scope Search Terms

SUSTAIN-6: An AKI Imbalances on Sema 0.5mg Is Not Surprising – Those Most Susceptible to Early GI AEs and AKI Only Get 0.5 mg in First 8 Weeks*

Semaglutide SUSTAIN-6 CVOT[1]: GI AEs Over Time



SUSTAIN-6[1] GI AEs

Sema 0.5 mg = 51%

Sema 1.0 mg = 52%

***For first 8 weeks**, all patients in both arms received semaglutide 0.5 mg dose;
Semaglutide 1.0 mg dose is not used until week 9 via titrations to limit GI AEs / AKI risk early on

0.5 mg Serious AKI Numeric Imbalance[1]:	30 AKI SAEs on 0.5 mg vs. 18 dose-matched placebo	3.1% vs 2.2%
0.5 mg Non-Serious + Serious AKI Imbalance[1]:	42 AKIs on 0.5 mg sema vs. 34 dose-matched placebo	5.1% vs 4.1%

1. EMA SUSTAIN-6 EPAR p.115: In the CVOT, "all AKI AEs and SAEs were associated with chronic renal disease [...] and some were temporally associated with GI AEs"

Wegovy (semaglutide) Has Clear AKI Imbalances in STEP-2 (Obesity + T2DM) & Other Trials But Approved With AKI Warnings

	Semaglutide 1.0 mg N = 402	Semaglutide 2.4 mg N = 403	Placebo Both Doses N = 402
Wegovy STEP-2 Total Serious AKIs	**2*** (0.5%)	**3*** (0.5%)	**1**** (0.2%)

- **Non-Serious AKIs Also Imbalanced in Step-2 & Other NDA Trials***: 5 (1.0%) on drug vs 2 (0.5%) on placebo**
- **Wegovy Has A 'New' AKI WARNING That Acknowledges: "Acute Kidney Injury occurred in clinical trials** in 7 adult patients (0.4 cases per 100 patient years) receiving WEGOVY® versus 4 patients (0.2 cases per 100 patient years of exposure) receiving placebo. Some of these adverse reactions occurred in association with GI adverse reactions or dehydration."

* AKI SAE narratives in CDER's review involve GI AEs/dehydration; One subject was titrating up in the 2.4mg arm. Subject was hospitalized twice with 2 AKI SAEs, both times involving GI AEs
** Placebo arm had one AKI SAE in either 1.0 mg arm or 2.4 mg arm; dose of placebo was not disclosed in FDA's medical review; imbalance was either 3 vs. 0 or 3 vs 1.
*** Wegovy NDA reviewer noted in public medical review that trials 4153, 4376, and 4374 also had additional serious AKI events on drug reported involving GI AEs and dehydration.
FDA Review Data Source: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2021/215256Orig1s000MedR.pdf (Page 37, Page 297, Page 304)

Another Wegovy (semaglutide) Serious AKI Imbalance Was Just Published Last Month In NEJM in Obesity + HF RCT

	Semaglutide 2.4 mg N = 263		Placebo 2.4 mg N = 266	
	N (%)	Events	N (%)	Events
Wegovy Total AKI SAEs	5 (1.9%)	6	1 (0.4%)	2

Wegovy AKI WARNING Is First To Acknowledge That: "Acute Kidney Injury occurred in clinical trials"

NEJM: Semaglutide in Patients with Heart Failure with Preserved Ejection Fraction and Obesity https://www.nejm.org/doi/full/10.1056/NEJMoa2306963?logout=true

AKI Risk Can Be Labeled, Monitored and Mitigated; GLP-1 Class AKI Warning for ITCA 650 Would Also Include Key Exenatide Aspects*

Current GLP-1 / Exenatide AKI Warnings – Applied To ITCA 650

Acute Kidney Injury Warning: exenatide may induce nausea, vomiting, and diarrhea with transient hypovolemia and may worsen renal function.

***Acute kidney injury has occurred in a ITCA 650 clinical trial** in 11 adult patients **(0.37 cases per 100 patient years of exposure receiving ITCA 650 versus 4 patients (0.14 cases per 100 patient years of exposure)** receiving placebo. Most reactions occurred in association with transient GI adverse reactions.

Risk Mitigation: Monitor renal function when initiating or escalating doses of ITCA 650 in patients with renal impairment reporting adverse gastrointestinal reactions.
Proactively advise patients of risk of AKI and the importance of keeping well hydrated if they experience any GI adverse reactions. Patients should also be instructed to call their healthcare provider right away if they have nausea, vomiting, or diarrhea that does not go away, as a loss of too much fluid (dehydration) may result in acute kidney injury. If dehydration occurs, stop suspected medications (including ITCA 650); treat dehydration.

This aligns with key aspects of exenatide (Byetta and Bydureon) acute kidney injury warnings. *Wegovy's AKI Warnings also notes AKI imbalances in clinical trials

Summary: GLP-1 GI AEs at Dose Initiation and Escalation are a Class Effect and an Established Risk Factor for Pre-Renal AKIs

- **Transient GI AEs GLP-1 class effect and an established risk factor for pre-renal AKIs[1,2]**
  - Transient GI AEs occur in a subset of patients on all GLP-1s at dose initiation and escalation[2]
  - Highest AKI risk in those with pre-existing renal impairment (common in CVOTs) [1,2]
- **AKI is monitorable and can be mitigated with labeling, monitoring, and proactive measures[3,4]**
  - Advise potential GI AEs at dose initiation/escalation, and risk of AKI if dehydration occurs
  - Advise to avoid dehydration if GI AEs occur; any evidence of dehydration, treat accordingly
  - Monitor renal function when clinically indicated and especially in renal impaired patients
  - If dehydration/renal impairment is evident, modify or stop suspected meds (incl. ITCA 650)
- **GLP-1 AKI Warning for ITCA 650 is justified based on data, precedence, and benefit/risk**
  - Ability to stop GLP-1 therapy is critical with any AKI SAE; when ITCA 650 is removed it eliminates drug levels in < 24 hours vs 5-8 weeks on long-acting injectable GLP-1s

1. AKI Imbalances: EMA EPAR Sustain-6 p. 115 and SUSTAIN-6 NEJM, 2016; Novo Nordisk LEADER EMDAC materials p. 75 of 95, ITCA 650 NDA; FDA's GLP-1 AKI Warnings For GLP-1 Class; 2. Bettge 2017; FDA GLP-1 Medical Reviews, Gorgojo-Martinez 2022; 3. Bettge 2017; 4. Wharton 2022.

Cardiovascular Safety: Meeting Pre- vs Post-Approval CVOT Requirements

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Issue #2 (MACE) Key Issues

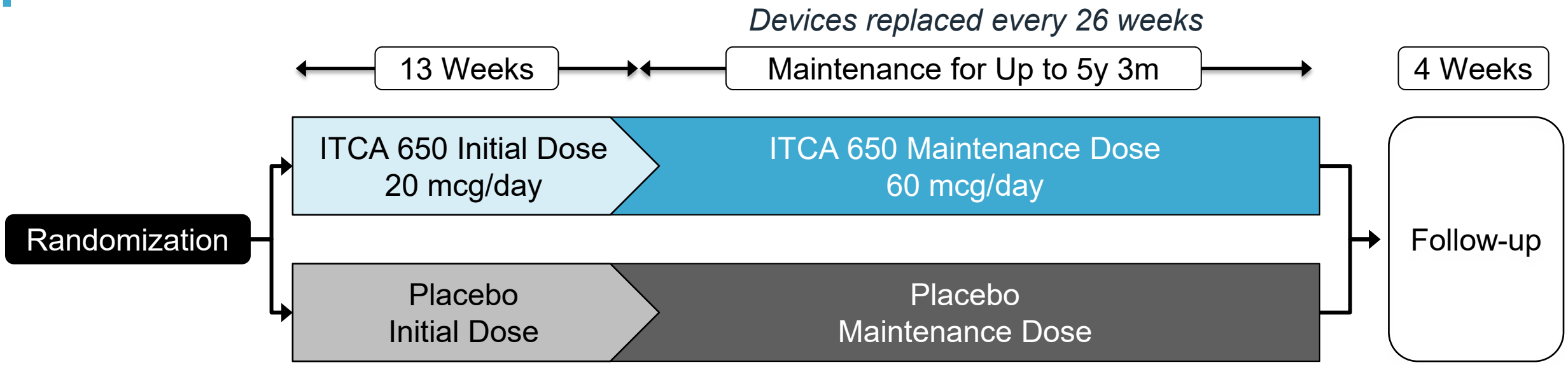
- Pre-approval CVOT meta-analysis met FDA's primary endpoint requirement to bridge to a definitive / longer post-approval CVOT
  - HR (95% CI) = 1.12 (0.83 – 1.51); non-Inferiority: p=0.002
- Pre-approval vs. post-approval CVOT cross-trial comparisons with different objectives, designs, power, and durations scientifically unsound
  - e.g. LEADER (N=9,340): 7.5x MACE and > 3x duration
- Post-hoc analyses of small subgroups/events have high type 1 error risks
  - Subject to incorrect / misleading conclusions
    - CV death in Study 107: 51 patients [28 (1.3%) vs 23 (1.1%)]
- GLP-1s / exenatide have not been shown to cause CV harm

2008 FDA Guidance on Evaluating CV Risk in Pre-Approval CVOTs

- Pre-approval: Preliminary safety analysis to exclude unacceptable risk
- Primary endpoint is upper bound of 95% CI for HR < 1.8 when comparing CV events for investigational agent to control group

- Supports use of 4- or 3-point MACE
- Meta-analysis of pre-approval studies permitted
- Once FDA's pre-approval CVOT endpoint met, a definitive (i.e., larger and longer CVOT) needs to be conducted post-approval to exclude an upper CI < 1.3

Study 107 (Pre-Approval CVOT): Design Preliminary Safety Assessment



- Diabetes Patient Population
- CV Risk Cohorts (High, Low)
- Event-driven study
- Primary analysis was meta-analysis of 4-point MACE* from Studies 103, 105, and 107
  - Median study duration 1.1 years
  - Median diabetes duration 10 years

*** CV Death, MI, CVA, or Unstable Angina resulting in hospitalization**

Primary Prespecified MACE Meta-Analysis Met Guidance Endpoint (Studies 107, 103 and 105)

	ITCA 650 N = 2,649	Placebo N = 2,502
Primary MACE: HR (95% CI) **p-value (for non-inferiority)**	**1.12** (0.83, 1.51) **0.002**	
MACE	**96 (3.6%)**	**85 (3.4%)**
Non-fatal MI	**35 (1.3%)**	**30 (1.2%)**
CV Death	**26 (1.0%)**	**21 (0.8%)**
Non-fatal stroke	**22 (0.8%)**	**21 (0.8%)**
Hospitalization for unstable angina	**13 (0.5%)**	**13 (0.5%)**

ITT/End of Study Population

Study 107 (Pre-Approval CVOT): While Not Primary Analysis, Also Met FDA's Criteria

	ITCA 650 N = 2,075	Placebo N = 2,081
Primary MACE: HR (95% CI) **p-value (for non-inferiority)**	**1.21** (0.90, 1.63) **0.004**	
MACE	**95 (4.6%)**	**79 (3.8%)**
Non-fatal MI	**37 (1.8%)**	**28 (1.3%)**
CV Death	**28 (1.3%)**	**23 (1.1%)**
Non-fatal stroke	**23 (1.1%)**	**23 (1.1%)**
Hospitalization for unstable angina	**12 (0.6%)**	**15 (0.7%)**

ITT/End of Study Population

Hazard Ratio for MACE Aligns with FDA's Powering Estimates with 181 Events

How 'Big' do Trials Need to Be?

Number of Events for 90% Power	Upper 95% CI Excluded	Maximum Point Estimate of HR	Patient-Years Needed (3% annual event rate)
88	2.0	1.32	2,933
122	1.8	1.26	4,067
256	1.5	1.17	8,533
611	1.3	1.11	20,367
4,627	1.1	1.04	154,233

CI: Confidence Interval; HR: Hazard Ratio

Pre-Approval Meta-analysis 181 MACE Events

FDA Presentation Slides, EMDAC Meeting October 24-25, 2018

Cross-CVOT Comparisons of Pre- vs Post-Approval CVOTs are Scientifically Unsound

	Pre-approval CVOT	Post-Approval CVOT
Design Goal	Rule out unacceptable increase in CV risk	Confirm CV safety
MACE Outcome	Exclude upper 95% CI of < 1.8	Exclude upper CI of < 1.3
Target Number of Events[1]	> 120 events Use of 4-point MACE and meta-analysis to increase events	> 610 events Typically use of 3-point MACE because adequately powered
Study Duration	Shorter (usually < 1.5 years) To short for CV benefit assessment	Longer (usually > 2 years) Can assess CV benefit
Enrollment Target	Smaller (usually N ~ 3000)	Larger (usually N > 6000)

1. FDA Presentation Slides, EMDAC Meeting October 24-25, 2018

Lixisenatide Showed Change in Pre-Approval vs Post-Approval MACE Results With More Events & Duration

	Lixisenatide N = 3,034	Placebo N = 3,034
Pre-Approval Interim Analysis: MACE + UA	140 **(4.6%)**	123 **(4.1%)**
HR (95% CI)	**1.14** (0.89, 1.47)	
Post-Approval Interim Analysis: MACE + UA	406 **(13.4%)**	399 **(13.2%)**
HR (95% CI)	**1.02** (0.89, 1.17)	

NDA on file

Post-Approval CVOT: Considerations

- Definitive CVOT design will be discussed with the FDA
  - Well powered and longer treatment duration for definitive safety
  - Assess secondary potential for CV benefit
- Enriched for
  - Elderly
  - Renal dysfunction (aligned with exenatide eGFR labeling)
  - Increased CV risk / disease
- Sufficient enrollment to complete trial in about 3.5 years*

*Subject to final trial size and minimal intended treatment duration following alignment/input from FDA

Summary: Post-Approval CVOT is Appropriate

- Pre-approval CVOT meta-analysis met FDA's primary endpoint requirements
- Approach known upfront to not be designed, powered or of sufficient duration for a definitive safety or superiority assessment
  - Significantly less power and duration than post-approval CVOTs
  - As expected, confidence intervals for MACE are wide
- Cross-trial comparisons of significantly different trial designs, power, durations, and patient populations are scientifically unsound
  - Do not replace prospective RCTs
- Larger, longer, post-approval CVOT is warranted and would be performed

Device & Inspectional Information Requests Already Addressed on Record

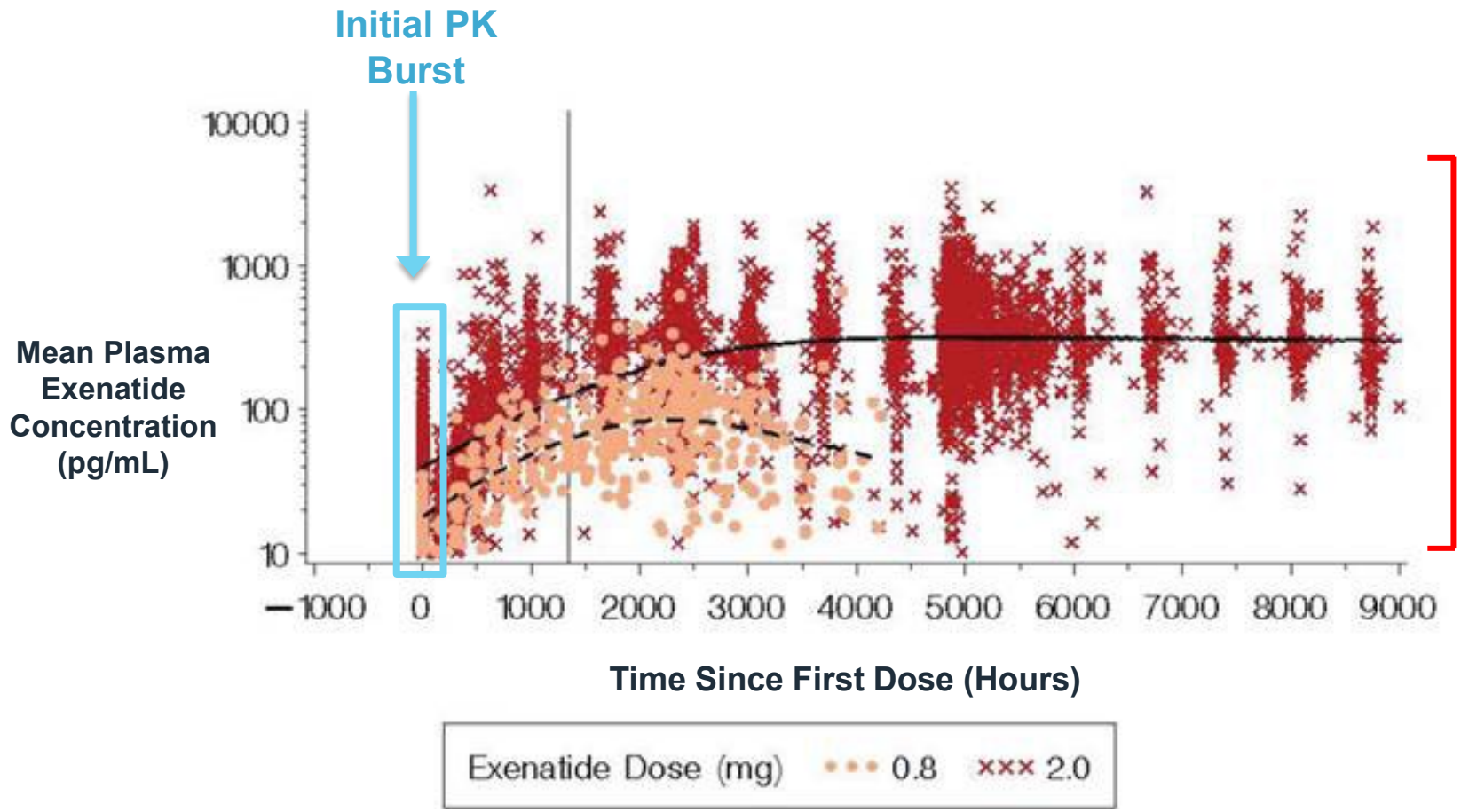
Kurt Graves

Chairman, President & CEO

Issue #3: Whether Clinical Data in 4 RCTs Validated Upper and Lower IVR Specification Limits as Effective and Safe

- Clinical data in 4 successful RCTs validate upper and lower in-vitro (IVR) limits of the implants
  - Unequivocal & sustained efficacy in all 4 trials
  - Safety in-line with GLP-1s and AKI labeled Warnings
- ITCA 650 implants performed as designed for intended 3- and 6-month therapy durations from in vitro release (IVR) tests

PK Context: Exenatide PK Variability is Well Known In Bydureon, Each Injection Has a PK Burst Followed by Significant Variability



~400-fold PK variability range from ~10 pg/mL to ~4000 + pg/mL at 2.0mg injection every week at steady state.

Outlier concentrations up to 11,652 pg/mL

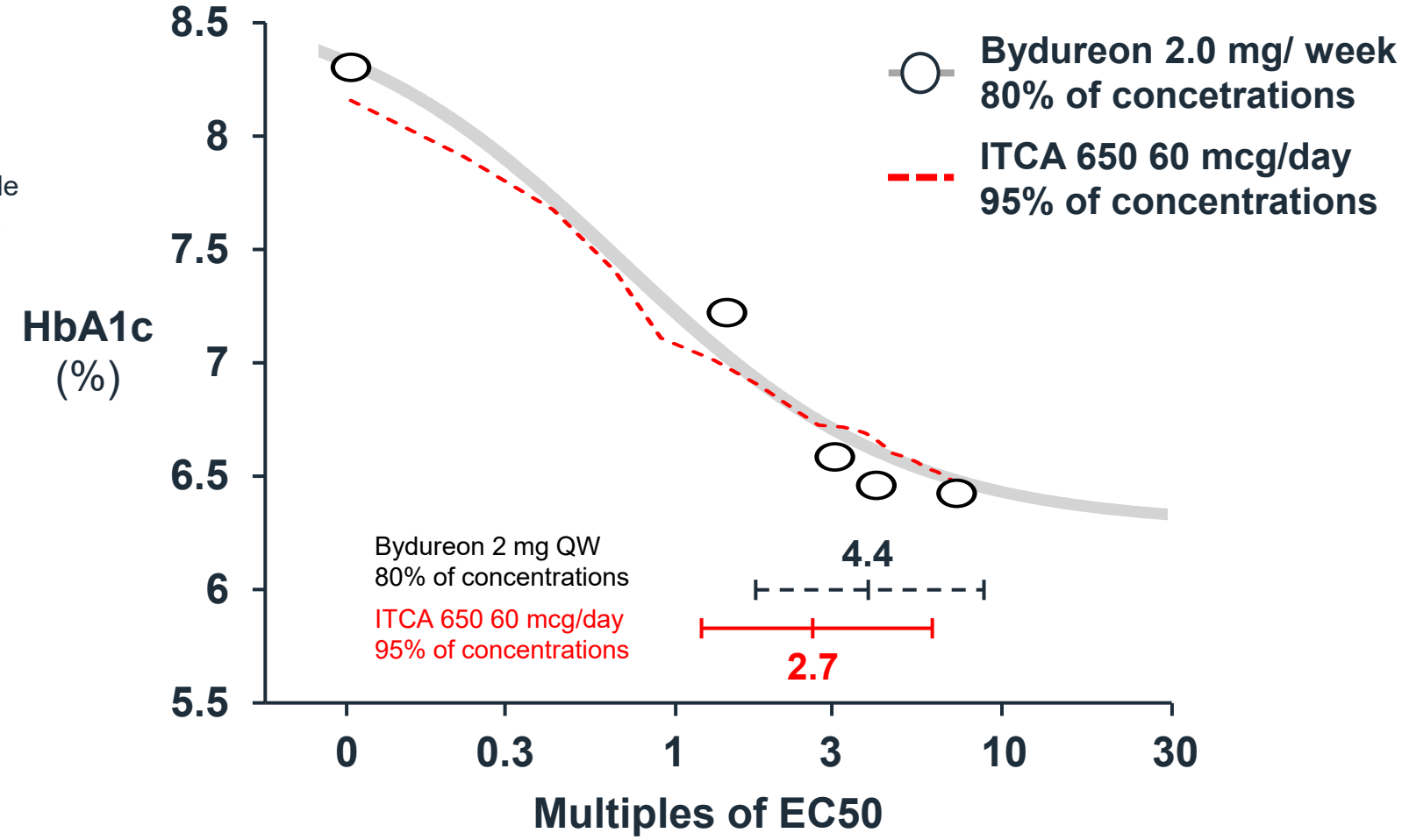
Despite this exenatide PK variability Bydureon is proven safe and effective

Cirincione B, Passarell J, Kothare P et al., poster at ASCPT 2009.
This figure was included in Section 2.7.2 as Figure 2.7.2-40 in the ITCA 650 NDA.

Exposure Response Data Modeled for ITCA 650 vs Bydureon Shows Less Variability for ITCA 650 Exposure

To accommodate potential differences in exenatide assays, reported exenatide concentrations for Bydureon and ITCA 650 were expressed as multiples of their respective EC50, a common unit of bioactivity.

The bars below the curves represent the middle 80% of concentrations for Bydureon 2 mg once-weekly and the middle 95% of concentrations for 60 mcg/day ITCA 650. This shows less PK variability for ITCA 650.



Data derived by digitizing the plots of HbA1c vs concentration in NDA Figure 2.7.2-37 and dividing concentrations by respective EC50 for ITCA 650 (126 pg/mL) and Bydureon (83.5 pg/mL). Gray curve is the best-fitting 3-parameter sigmoid for the Bydureon data. Original source for Bydureon data: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000ClinPharmR.pdf (pg 9 of 44, Figure 3).

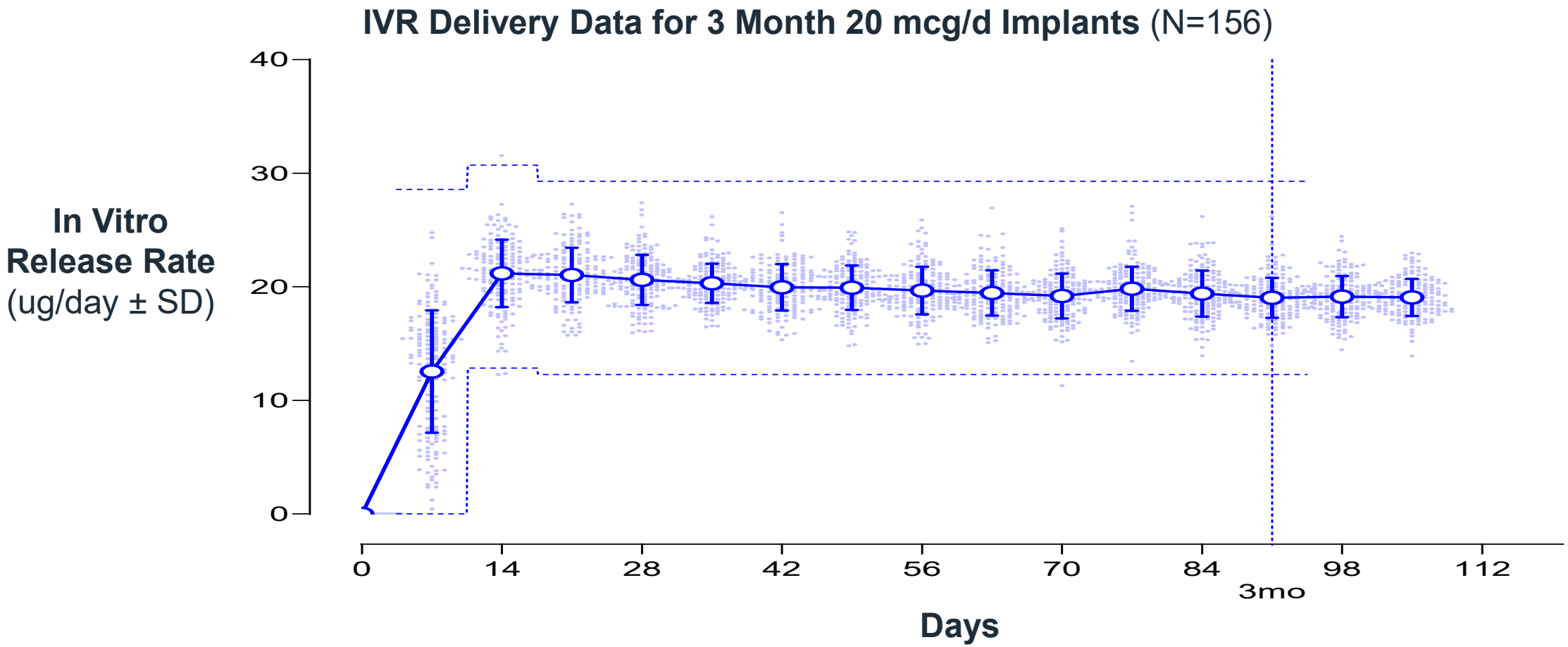
ITCA 650 Implants Performed Within Pre-Specified Upper And Lower Limits of Device IVR Specifications

	1st Startup Interval[1]		2nd Interval[1]		3rd Interval[1]		4th Interval[1]		5th Interval[1]		6th Interval[1]	
	Range (mcg)	% Variability	Range (mcg)	% Variability	Range (mcg)	% Variability	Range (mcg)	% Variability	Range (mcg)	% Variability	Range (mcg)	% Variability
20 mcg/day implants	5 – 190	± 94.8	105 – 200	± 31.2	100 – 190	± 26.7	100 – 190	± 26.7	100 – 190	± 26.7	100 – 190	± 26.7
60 mcg/day implants	420 – 980	± 40.0	715 – 1075	± 20.1	640 – 1025	± 23.1	640 – 1025	± 23.1	640 – 1025	± 23.1	640 – 1025	± 23.1

Extensive ITCA 650 clinical data from 4 successful RCTs validate these pre-specified upper and lower IVR limits unequivocally effective in all 4 trials, with safety profile in-line with GLP-1s & existing AKI Warnings

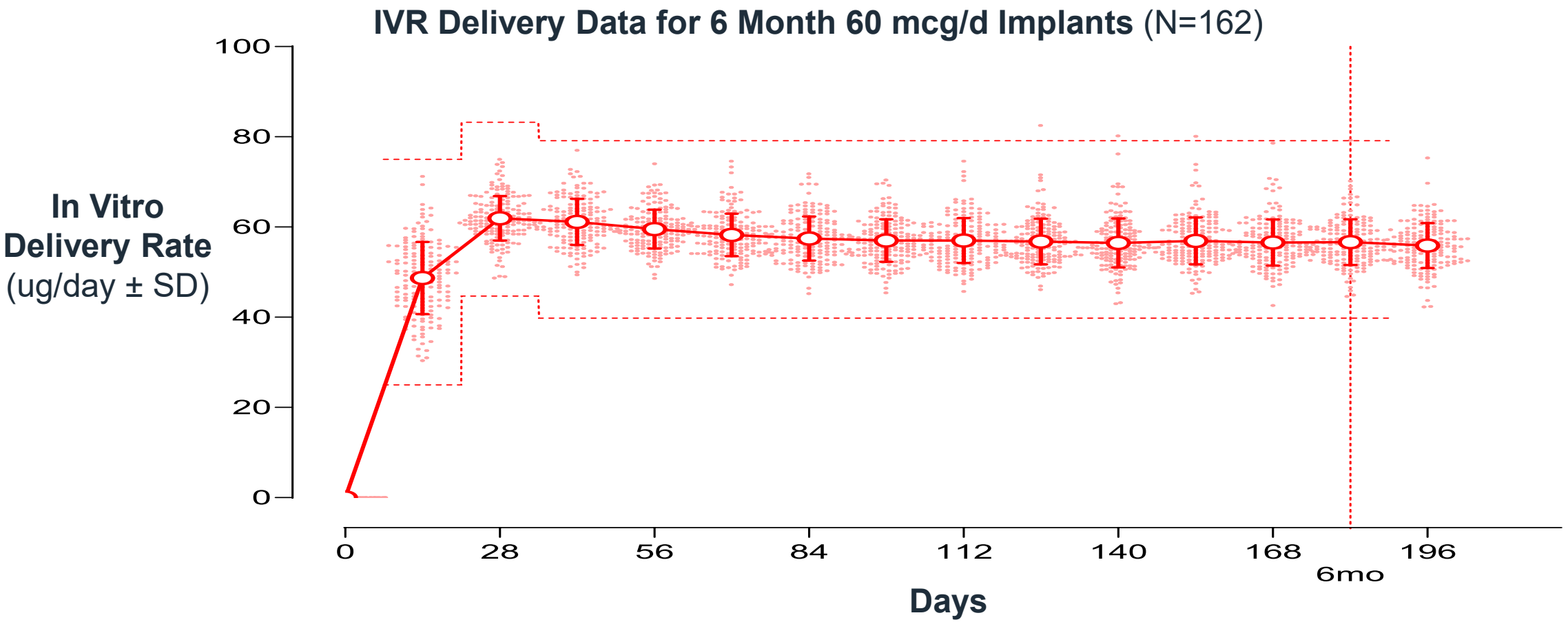
1. Each of 6 Intervals are every 7 days for 20 mcg/day devices, and every 14 days for 60 mcg/day devices

ITCA 650 Three Month Implants: IVR Data on Multiple Lots Show Consistent Delivery Within Set Upper and Lower IVR Limits[1]



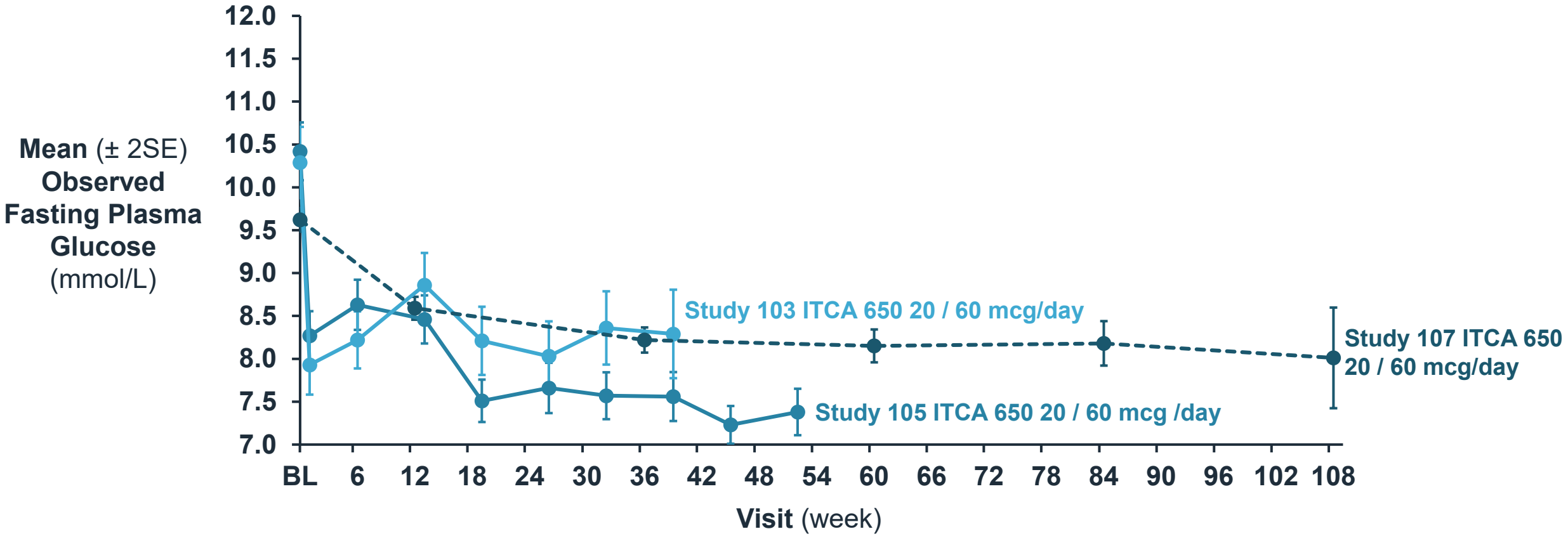
1. <USP 724>: Phase 3 / Registration Lots C1508561, C1609000, and C1609271; N= 156 implants and 2,028 datapoints tested during the stability study (from T=0 to T=24 months at 25C); No <USP 724> level 3 outliers

ITCA 650 Six Month Implants: IVR Data on Multiple Lots Show Consistent Delivery Within Set Upper and Lower IVR Limits[1]



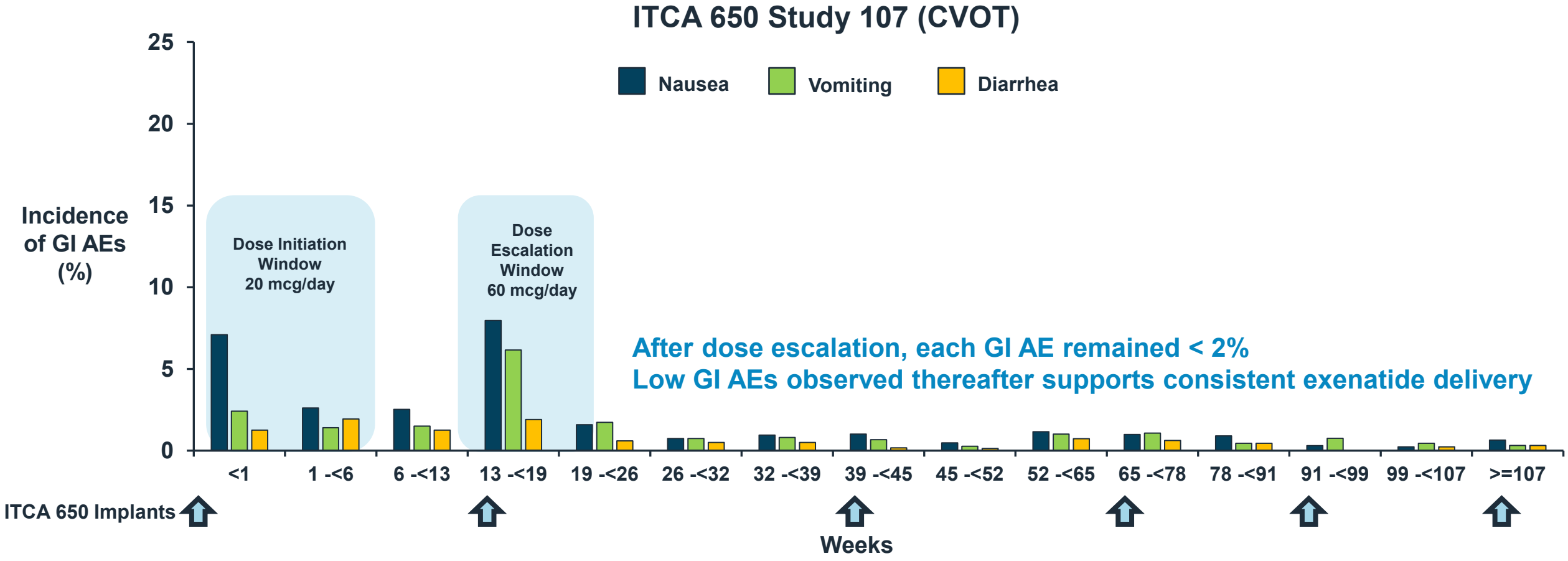
<USP 724>: Phase 3 / Registration Lots C1508680, C1609142, and C1609261; N= 162 implants and 2,100 datapoints tested during the stability study (from T=0 to T=24 months at 25C); No <USP 724> level 3 outliers

ITCA 650 Fasting Plasma Glucose Data in Phase 3 RCTs Show Devices are Performing as Designed for Intended Durations



Visit (week)	BL	1	6	12	13	19	26	32	36	39	44	52	60	84	108
Study 103 ITCA 650	153	145	148	-	147	140	130	124	-	125	-	-	-	-	-
Study 105 ITCA 650	265	253	256	-	250	238	228	216		209	205	204	-	-	-
Study 107 ITCA 650	2,063	-	-	2,012	-	-	-	-	1,646	-	-	-	1,021	511	90

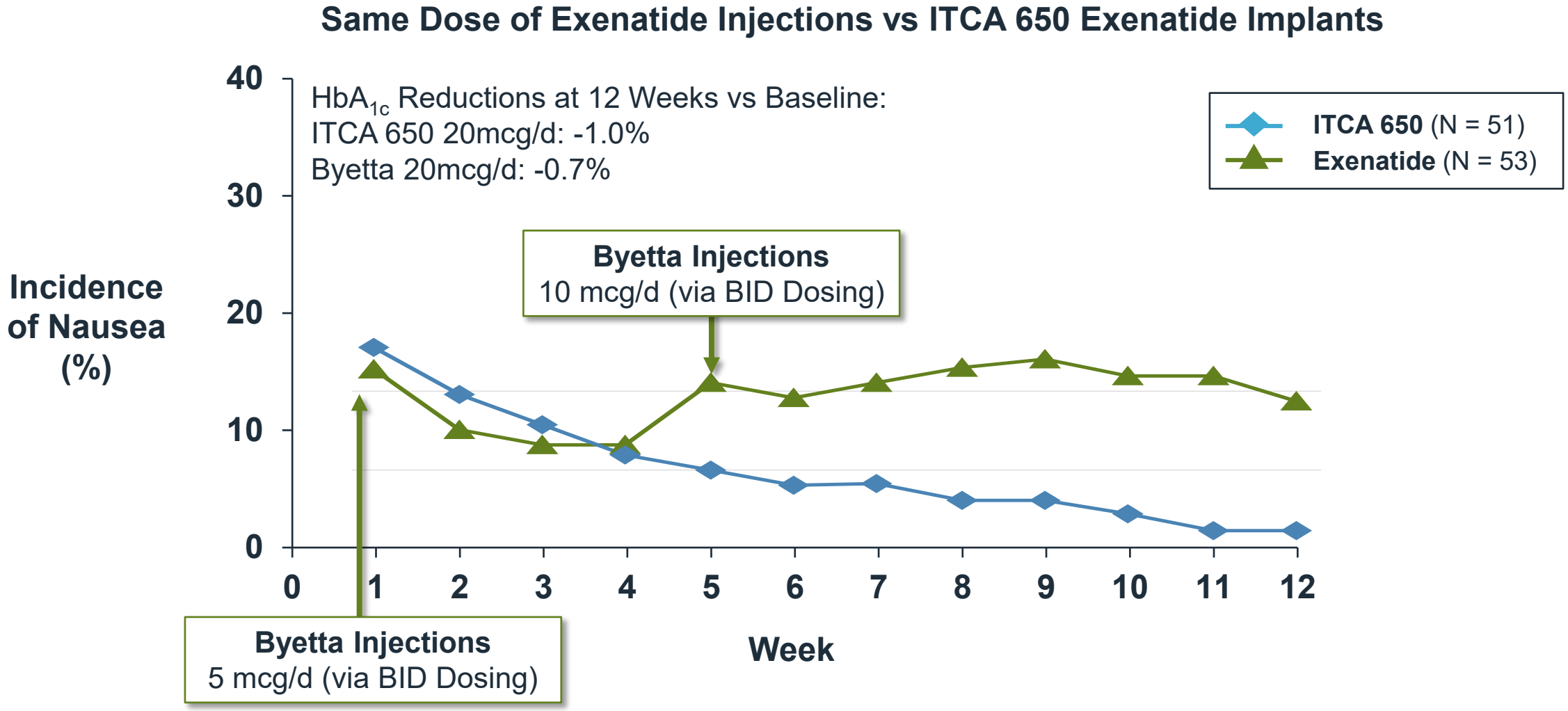
ITCA 650, Like all GLP-1s, Causes Some Transient GI AEs at Dose Initiation/Escalation; Low GI AEs After Shows Implant Consistency



N of Patients

ITCA 650	2070	2064	2060	2048	2022	2008	1993	1781	1481	1373	1117	884	658	439	308

Head-to-Head Trial Validated IVR Specifications Showing Improved GI Tolerability of ITCA 650 Implants vs Exenatide Injections



ITCA 650 NDA: Phase 2 Trial done to confirm comparative tolerability and efficacy of exenatide starting dose for Phase 3 Trials

Benefit / Risk & GLP-1 Class Labeled AKI

Patient Needs And NDA Data Support Positive Benefit-Risk for ITCA 650 with Class-Labeled AKI Warning and Post Approval CVOT

✓ Extended Maintenance Therapy Option Needed

- Uncontrolled HbA_{1c} is a crisis in > 50% patients
- Often caused by non-adherence and non-persistence to injections
- New extended maintenance dosing options are needed

✓ Unequivocal Sustained Efficacy with 6-Month Dosing

- 4 successful Phase 3 trials
  - > 5,800 T2DM patients
  - > 22,000 implants
- Consistent and highly effective exenatide delivery
  - Improved HbA1c
  - Improved weight loss
- Only twice-yearly dosing
- Clinical data validated IVR limit specifications as effective and safe for intended / labeled use

✓ Safety In-Line with GLP-1s, and Label

- GI AEs rates in-line with class, majority at dose initiation and escalation
- GI AEs and AKIs GLP-1 class effects seen in post-marketing reports, and more RCT AKI Imbalances
- GLP-1s carry Warnings and Risk Mitigation for AKI
- Met FDA's pre-approval CVOT requirements

ITCA 650's Safety is In-Line with GLP-1 Class and Supported by Labeling and Risk Mitigations

✓ Risk Mitigations and Post-Marketing Commitment

- Class label AKI Warnings and risk mitigations
- Not self-administered; only given by trained and certified HCPs
- In-office education and mitigation materials will inform patients of GI AEs / dehydration and AKI risks and what to do with their provider
- Post-approval CVOT well powered with longer-duration needed to confirm both CV safety, potential CV benefit, and renal outcomes

Former ADA Presidents and 12 Top Diabetes Experts Note AKI is a Class Effect in RCTs, CV Harm is Biologically Implausible… And That Twice-Yearly ITCA 650 is Needed

UNC SCHOOL OF MEDICINE

Saturday, September 9, 2023

Dear Advisory Committee members:

We would like to call your attention to our letter of August 20th, 2020, to Dr. Peter Stein, Director of the Office of New Drugs (CDER). We have been members of Intarcia's Scientific Advisory Board and reflected on the issues at the heart of today's hearing in detail three years ago. We would like to reaffirm:

1. Despite all the advances in GLP-1RA therapy, ITCA 650 will address an unmet need for many patients with type 2 diabetes. Adherence promotion with every 6-month implant administered in a provider's office will help address unresolvable barriers to the most effective class of antihyperglycemic medication in diabetes care for many people living with the disease.
2. The issue of imbalances in AKI events with GLP-1RA is well known and has been repeatedly demonstrated in published randomized trials and post marketing reports. It has become part of standard teaching in professional education. There is no meaningful difference in the ITCA 650 record in this regard that differentiates it in the class.
3. The CV data for ITCA 650 meets all regulatory guidance for marketing approval with a post-marketing study to further narrow the confidence interval around MACE events. The GLP-1RA class effect, the effect of exendin-4 based peptides, and the effect of exenatide is well studied and established. It is biologically implausible that ITCA 650 is associated with cardiovascular harm.

As long-standing clinical investigators and leaders in diabetes care and practice, we strongly encourage the FDA to provide marketing authorization for ITCA 650 with a post-marketing CV outcome trial and a class-labeled AKI Warning and risk mitigations around AKI prevention. Our prior letter is part of the FDA record for this product, but it is attached for convenience. Thank you for your careful attention and deliberation on behalf of the 30 million people living with diabetes in the United States.

Sincerely,

John B. Buse, MD, PhD
Verne S. Caviness Distinguished Professor
Director, Diabetes Care Center
Director, NC Translational and Clinical Sciences Institute
Senior Associate Dean for Clinical Research
University of North Carolina at Chapel Hill

Ralph A. DeFronzo, MD
Professor of Medicine
Chief, Diabetes Division
University of Texas Health Science Center
Deputy Director, Texas Diabetes Institute

Daniel J Drucker M.D.
Professor of Medicine
Mt. Sinai Hospital, Senior Scientist Lunenfeld Tanenbaum Research Institute
University of Toronto

Steven Edelman MD
Clinical Professor of Medicine
University of California San Diego
Veterans Affairs Medical Center
Founder and Director "Taking Control of Your Diabetes"

Vivian Fonseca MD
Professor of Medicine and Pharmacology
Assistant Dean for Clinical Research
Tullis Tulane Alumni Chair in Diabetes
Chief, Section of Endocrinology
Tulane University Health Sciences Center

James R. Gavin III, MD, PhD
Clinical Professor of Medicine, Emory University School of Medicine
Chief Medical Officer, Healing Our Village, Inc

Steven E. Kahn, M.B., Ch.B.
Professor of Medicine
Leonard L. Wright and Marjorie C. Wright Chair
Division of Metabolism, Endocrinology and Nutrition
Director, Diabetes Research Center
University of Washington

Harold E. Lebovitz, MD
Professor of Medicine, SUNY Downstate Medical Center

William H. Polonsky, PhD, CDCES
President, Behavioral Diabetes Institute
Associate Clinical Professor, University of California, San Diego

Julio Rosenstock, MD
Director, Dallas Diabetes Research Center at Medical City
Clinical Professor of Medicine, University of Texas Southwestern Medical Center

Jay S. Skyler, MD, MACP
Professor of Medicine, Pediatrics, & Psychology
Division of Endocrinology, Diabetes, & Metabolism
Deputy Director, Diabetes Research Institute
University of Miami Miller School of Medicine

ITCA 650

Intarcia Therapeutics (Business Unit of i2o Therapeutics)

Endocrinologic and Metabolic Drugs Advisory Committee

Sept 21, 2023

Slides for the Record

Issue #4: Device Failure Risk Factual Inaccuracies

CDER: Failure rate of [1.46%] inadequate to support safety and effectiveness; Inadequate mitigation strategies to reduce device failures

dFMEA work identified risks mitigated to 0.26%.

This also involved moving from manual to automated manufacturing steps for scale up

Device Failure Risks	Post-dFMEA Work and Change from Manual to Automated Manufacturing (1,170 Devices)
Total	**0.26%**
Early piston stoppage	0 (0%)
Inconsistent delivery within specs	1 (0.09%)
Early exhaustion (at end of device duration)	2 (0.17%)

* dFMEA = Design failure mode and effect analysis (DFMEA)

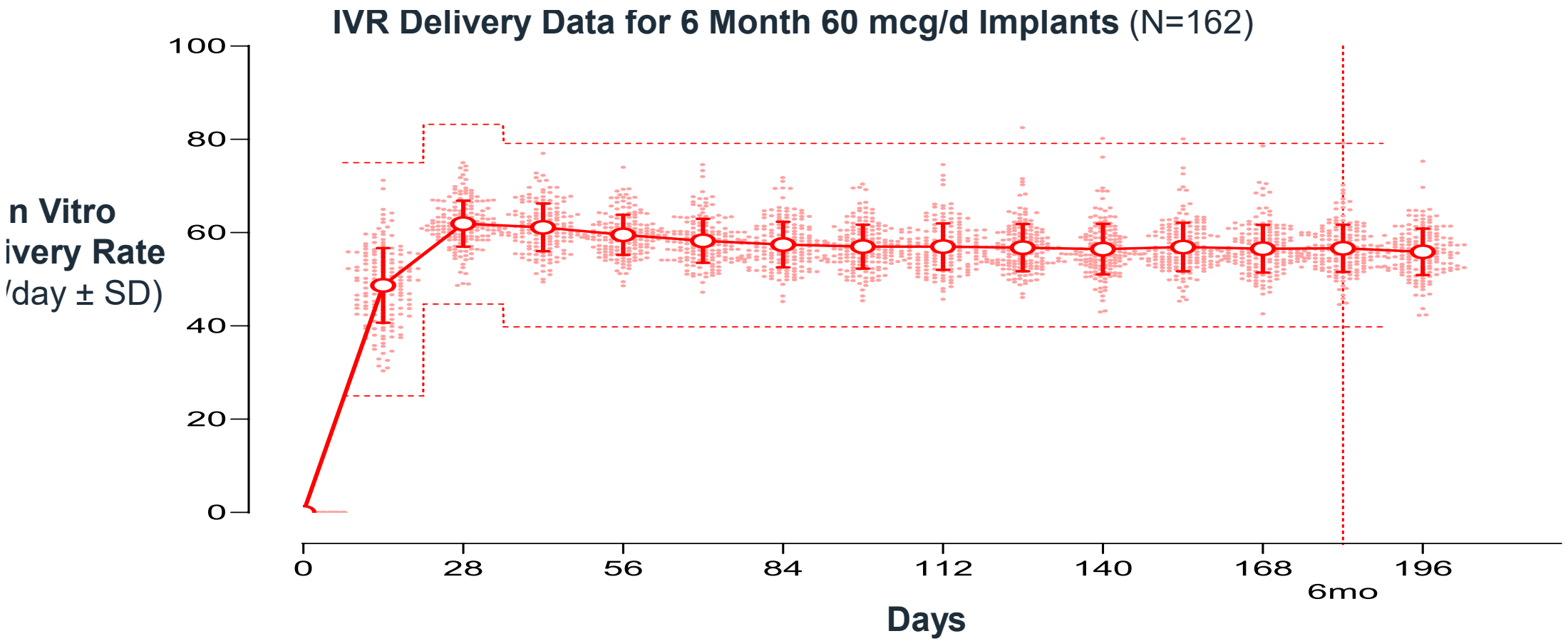
Issue #5: Well Documented Sterility, Corrective Actions / Clarifications Have Been Addressed on Record

CDER: Container-closure integrity test (CCIT) data used for intermediate sterile components	*CDER: Product-contact filling equipment used for commercial manufacturing*	*CDER: Routine depyrogenation process for components of primary container-closure system*	*CDER: Method suitability data provided to support proposed routine endotoxins test method*
Sterility tests passed per protocol and fully maintained integrity of multi-layer sterile barrier. NDA facts on record	**Filler manifold was a planned future change clarified at PAI inspection; Confirmatory sterility test done successful. NDA facts on record**	**Depyrogenation process completed documented and filed successfully. NDA facts on record**	**Endotoxin method validation completed, and FDA reviewed successfully. NDA facts on record**

Issue #6: Well Documented Quality Control, Corrective Actions / Clarifications Addressed on Record

CDER: Controls inadequate to ensure empty devices not included in final release	*CDER: Qualification of filling line with original or new manifold not performed*	*CDER: The results of the process simulation test (PST), used to demonstrate effectiveness of preventing microbiological contamination of ITCA 650, were not provided.*
Zero evidence of empty device in entire program with thousands of devices Robust device filling controls documented and utilized.	**Mistake, CDER assumed use of new filler manifold. A planned/permitted future change post-approval for added scale-up**	**All process simulation tests (PSTs) for sterility / manufacturing product passed. PST evidence provided to CDER on 03-05-2020**

Back-up Slides Shown



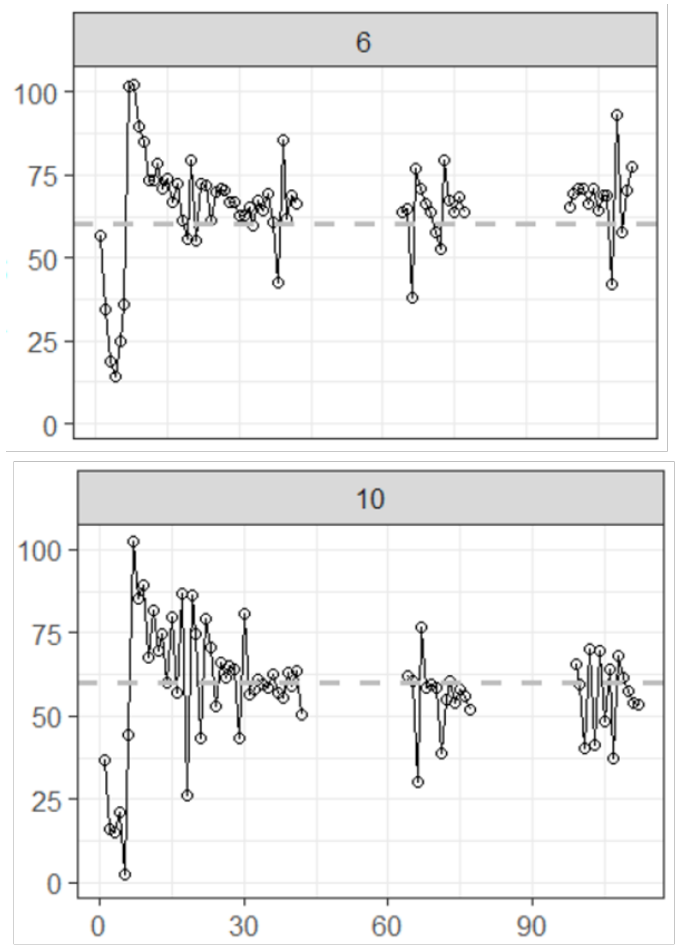
724>: Phase 3 / Registration Lots C1508680, C1609142, and C1609261; N= 162 implants and 2,100 datapoints tested during the stability study (from T=0 to T=24
ıs at 25C); No <USP 724> level 3 outliers

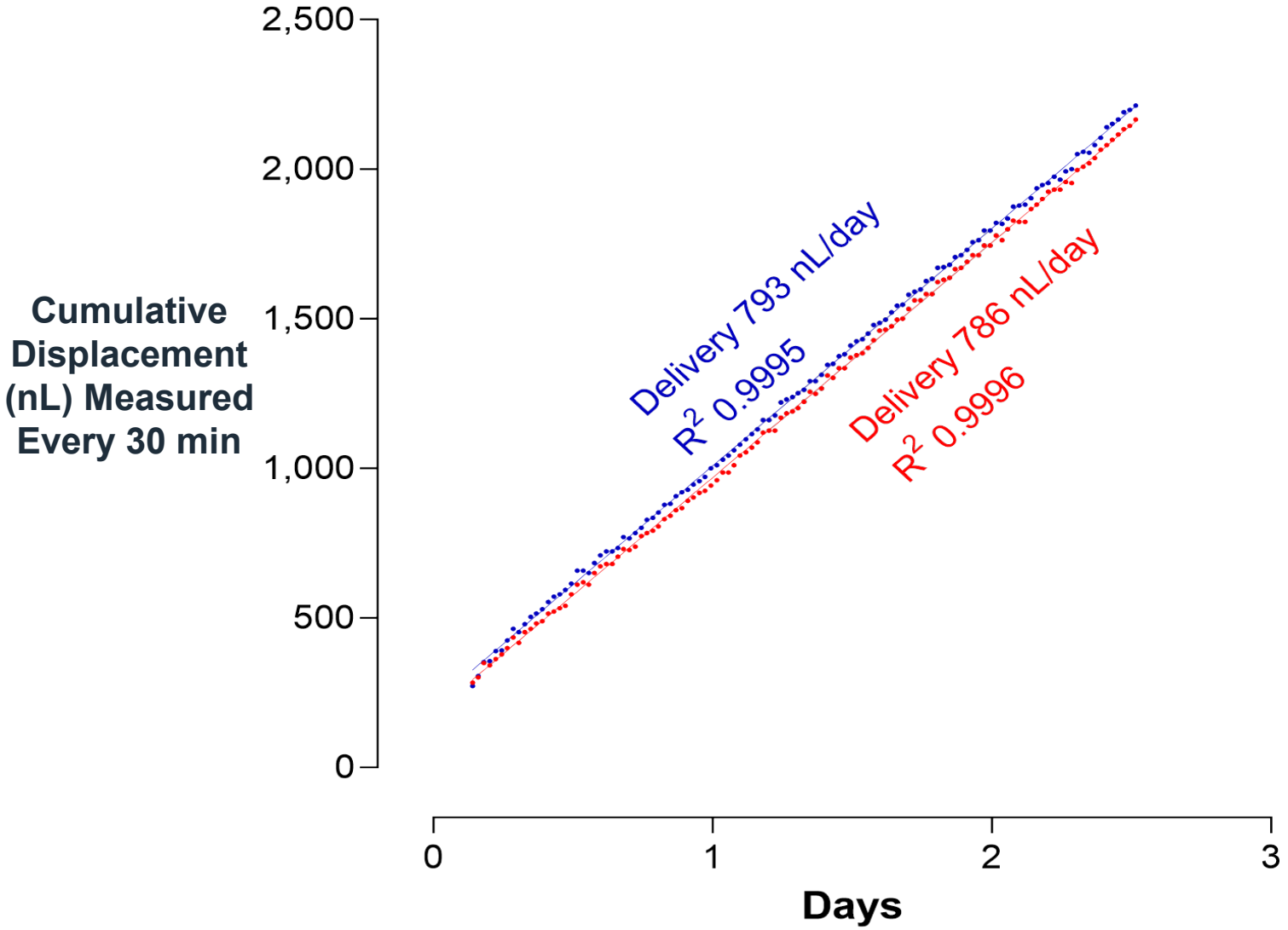
Daily IVR Method Has Limitations When Trying To Measure Only 0.8µL Per Day; Introduces Variability

- Low daily volume (0.8µL) complicates day-to-day measurement
- Potential for small fractions of (0.8µL) to carry over day-to-day
  - Exenatide concentrations measured in capture chamber
- Supports use of weekly measurement but challenging for daily due to such small amounts measured day-to-day

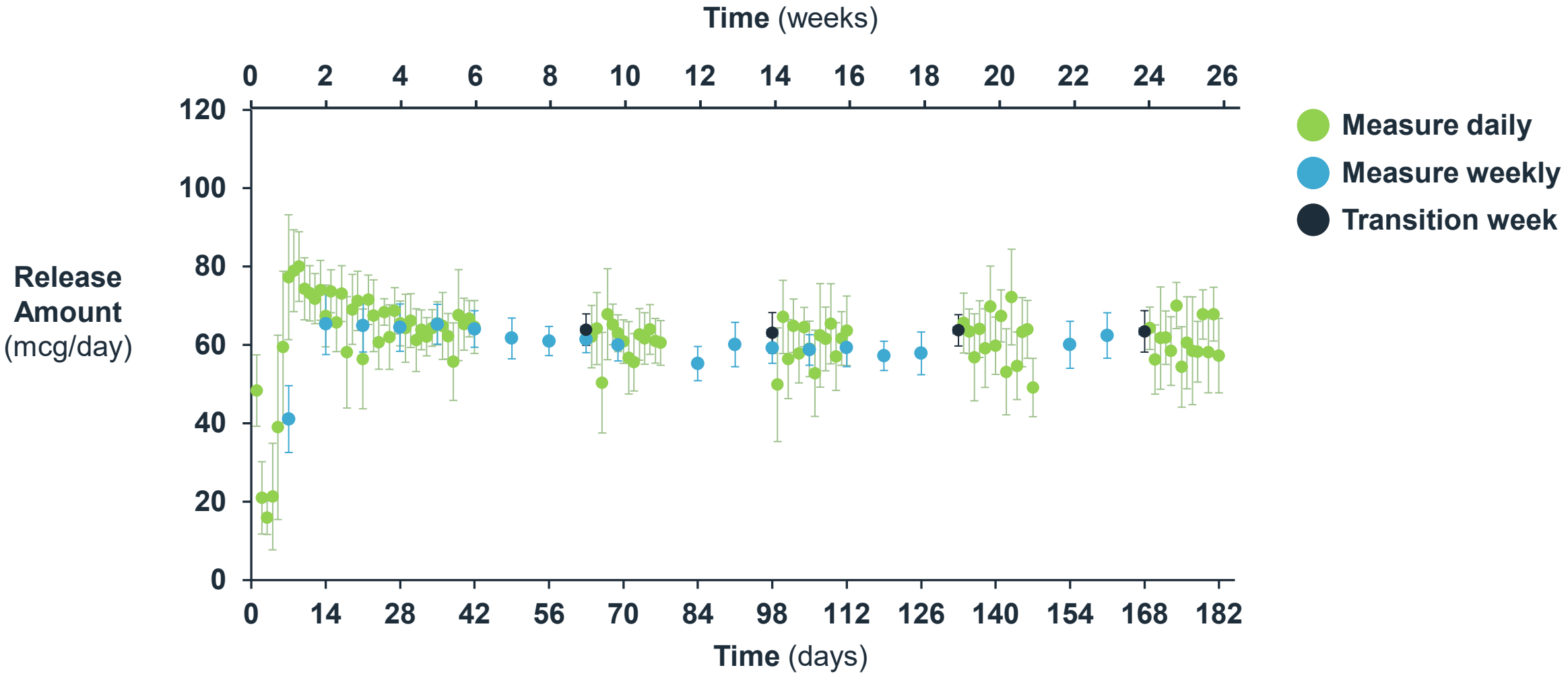
Variability is Consistent, Day to Day Variability Seen in FDA Figures Due to Method of Collection

FDA IVR Plots



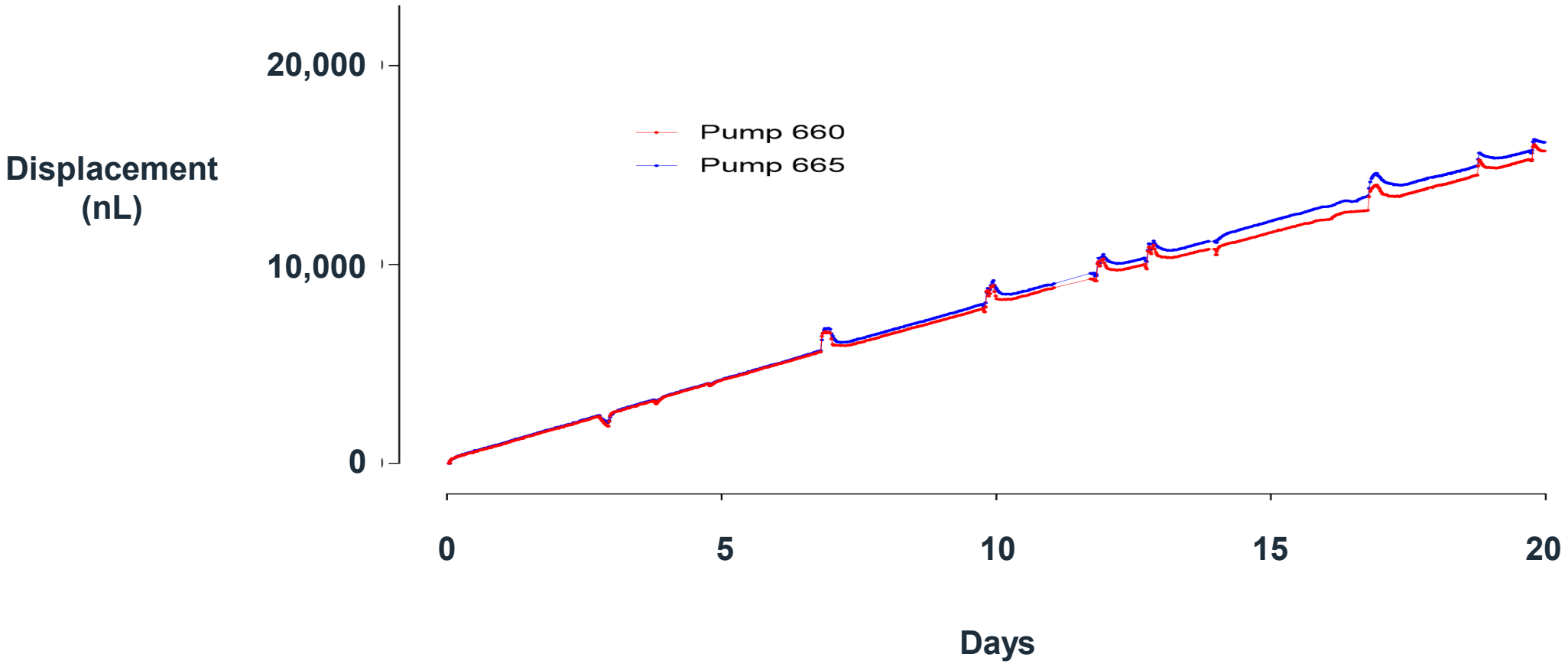


ITCA 650: IVR Continuous Release Data Within Pre-Specified Upper and Lower Limits; Weekly and Daily

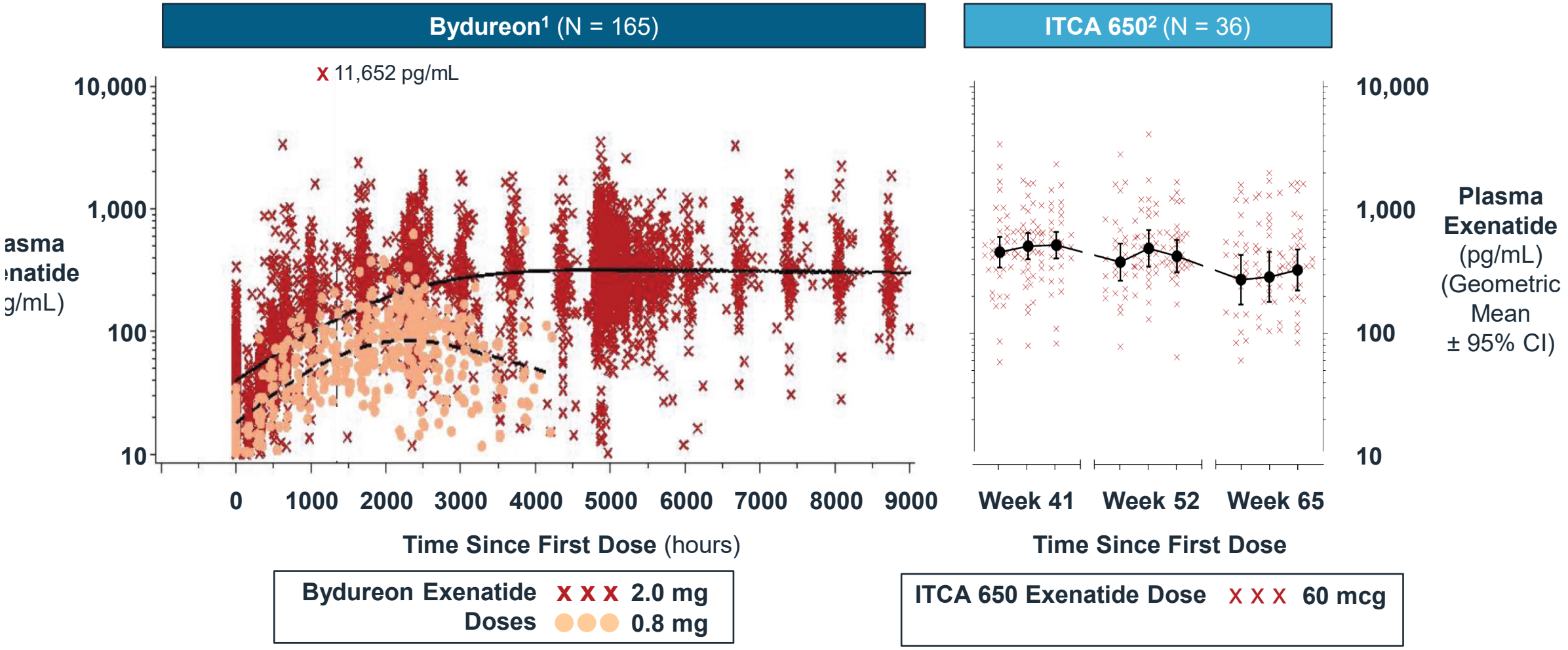


Design Verification by Daily IVR (Provided in Resubmission) *Lot C1609261, nominal 60 mcg/day for 6 months*

Individual Device Delivery Maintained over Weeks



Comparable Exenatide PK Variability for Bydureon and ITCA 650



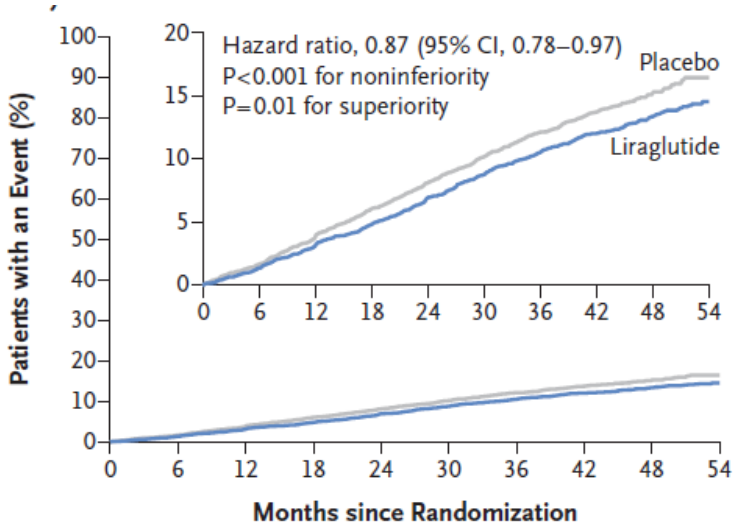
incione B, Passarell J, Kothare P et al., poster at ASCPT 2009.
lividual PK samples collected on 3 consecutive days for patients in Study 103SS with ITCA 650 60 mcg device in place

Sensitivity Analyses for Primary CV Outcomes

		ITCA 650	Placebo	Hazard Ratio (95% CI)
Meta-Analysis	**MACE 4**			
	ITT Population Censoring Based on EOS	96/2,649 **(3.6%)**	85/2,502 **(3.4%)**	**1.12** (0.83, 1.51)
	mITT-1 Population Alternate Censoring Based on EOT	83/2,641 **(3.1%)**	71/2,493 **(2.8%)**	**1.20** (0.88, 1.65)
	mITT-1 Population Alternate Censoring Based on EOT + 30 Days	86/2,641 **(3.3%)**	77/2,493 **(3.1%)**	**1.14** (0.84, 1.56)
	MACE 3			
	ITT Population Censoring Based on EOS	85/2,649 **(3.2%)**	75/2,502 **(3.0%)**	**1.13** (0.83, 1.54)
	mITT-1 Population Alternate Censoring Based on EOT	73/2,641 **(2.8%)**	61/2,493 **(2.4%)**	**1.24** (0.88, 1.74)
	mITT-1 Population Alternate Censoring Based on EOT + 30 Days	77/2,641 **(2.9%)**	67/2,493 **(2.7%)**	**1.18** (0.85, 1.64)
Study 107	**MACE 4**			
	ITT Population Censoring Based on EOS	95/2,075 **(4.6%)**	79/2,081 **(3.8%)**	**1.21** (0.90, 1.63)
	mITT-1 Population Alternate Censoring Based on EOT	82/2,070 **(4.0%)**	66/2,074 **(3.2%)**	**1.29** (0.93, 1.79)
	mITT-1 Population Alternate Censoring Based on EOT + 30 Days	85/2,070 **(4.1%)**	71/2,074 **(3.4%)**	**1.24** (0.91, 1.70)
	MACE 3			
	ITT Population Censoring Based on EOS	85/2,075 **(4.1%)**	69/2,081 **(3.3%)**	**1.24** (0.90, 1.70)
	mITT-1 Population Alternate Censoring Based on EOT	73/2,070 **(3.5%)**	56/2,074 **(2.7%)**	**1.36** (0.96, 1.92)
	mITT-1 Population Alternate Censoring Based on EOT + 30 Days	77/2,070 **(3.7%)**	61/2,074 **(2.9%)**	**1.31** (0.94, 1.83)

Primary MACE Outcomes for Other GLP-1s Shows Separation Primarily After 1 Year

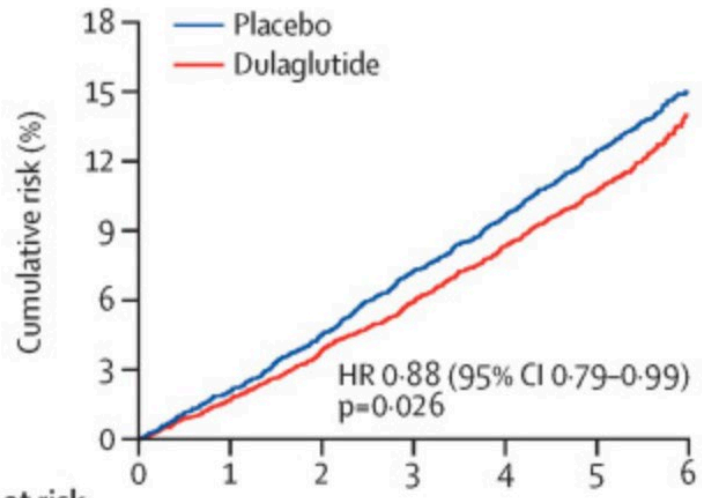
LEADER (liraglutdide)[1]



No. at Risk

Liraglutide	4668	4593	4496	4400	4280	4172	4072	3982	1562	424
Placebo	4672	4588	4473	4352	4237	4123	4010	3914	1543	407

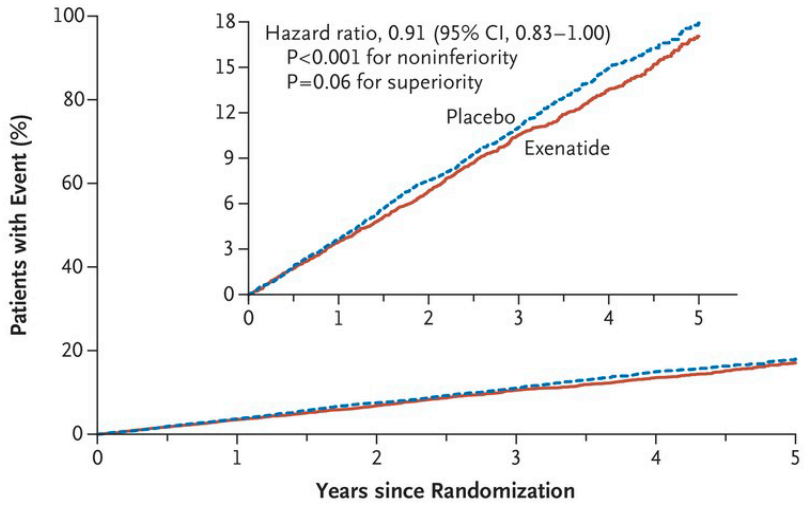
REWIND (dulaglutide)[2]



Number at risk

Placebo	4952	4791	4625	4437	4275	3575	742
Dulaglutide	4949	4815	4670	4521	4369	3686	741

EXSCEL (exenatide)[3]

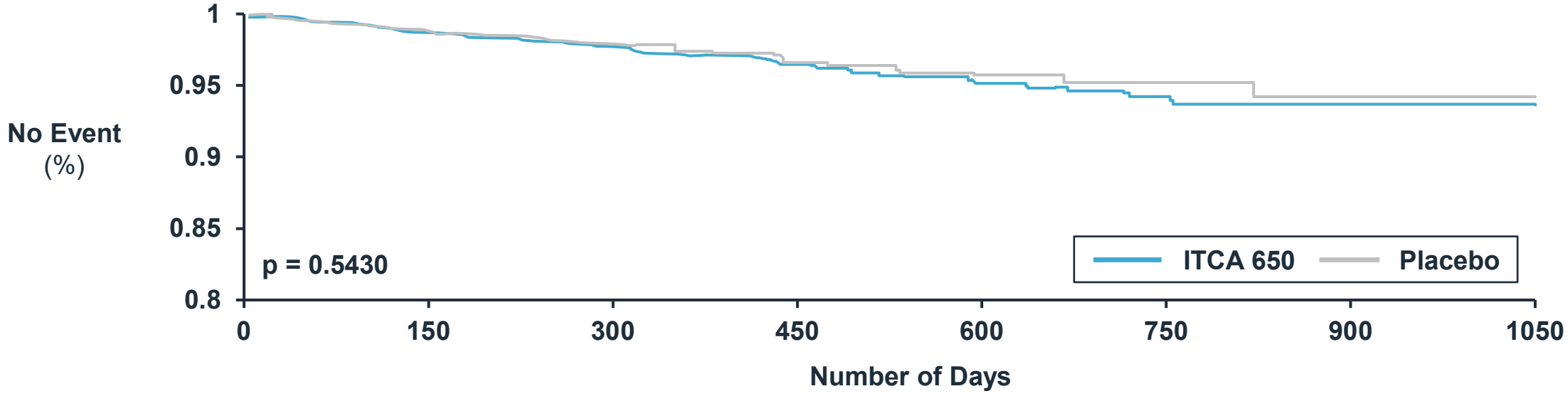


No. at Risk

Placebo	7396	7120	6897	6565	5908	4468	3565	2961	2209	1366	687
Exenatide	7356	7101	6893	6580	5912	4475	3595	3053	2281	1417	727

1. Verma, 2018; 2. Gerstein et al. (2019); 3. Holman, 2017.

Meta-Analysis: Primary CV Outcome Analysis



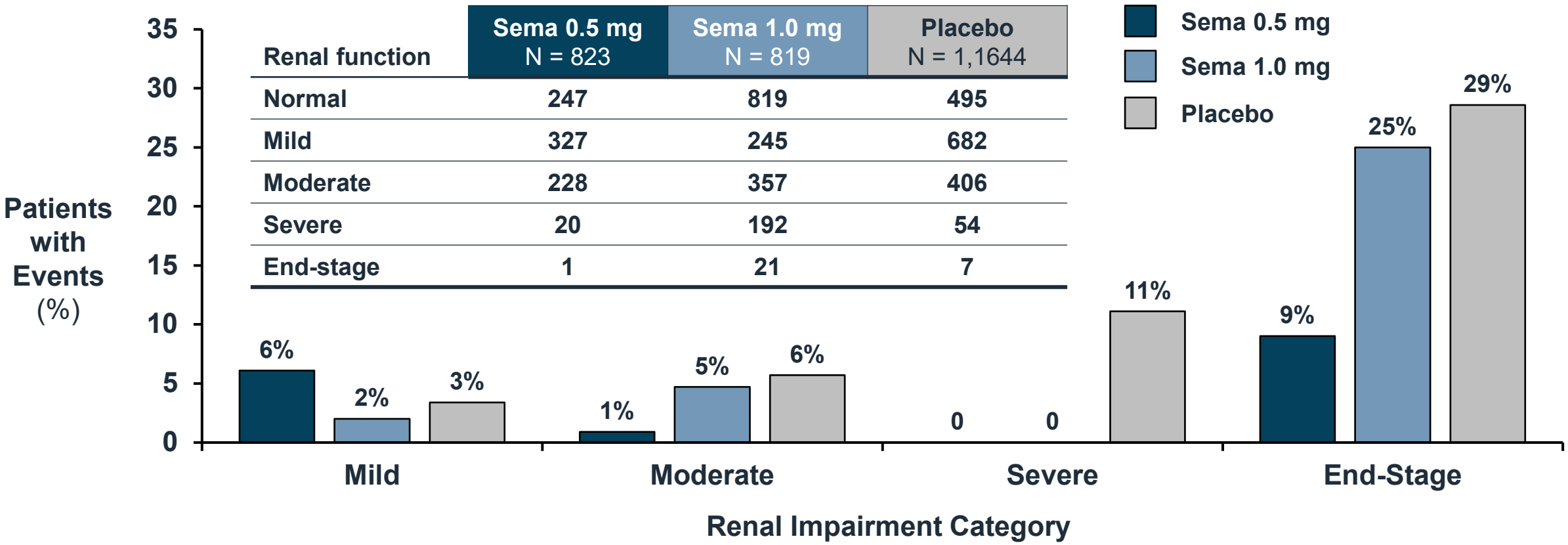
Number of Patients at Risk

ITCA 650	2649	2604	2120	1163	785	320	39	0
Placebo	2502	2460	2001	1168	789	337	47	0

Composite Endpoint Analysis	ITCA 650 n/N (%) per 100 PY	Placebo n/N (%) per 100 PY	Hazard Ratio (95% CI)	P-value
Primary CV Outcome: Time to First Occurrence of MACE1 Composite Endpoint				
Pooled Studies – ITT Population – Primary CV Outcome Analysis: Censoring based on EOS	96/2649 **(4%)/2.8**	85/2502 **(3%)/2.56**	**1.123** (0.834, 1.513)	**0.002** (non-inferiority)
Study 107 – ITT Population – Primary CV Outcome Analysis: Censoring based on EOS	95/2075 **(5%)/3.29**	79/2081 **(4%)/2.72**	**1.209** (0.897, 1.630)	**0.212**

SUSTAIN 6: AKI Data in Normal Renal Function is Missing

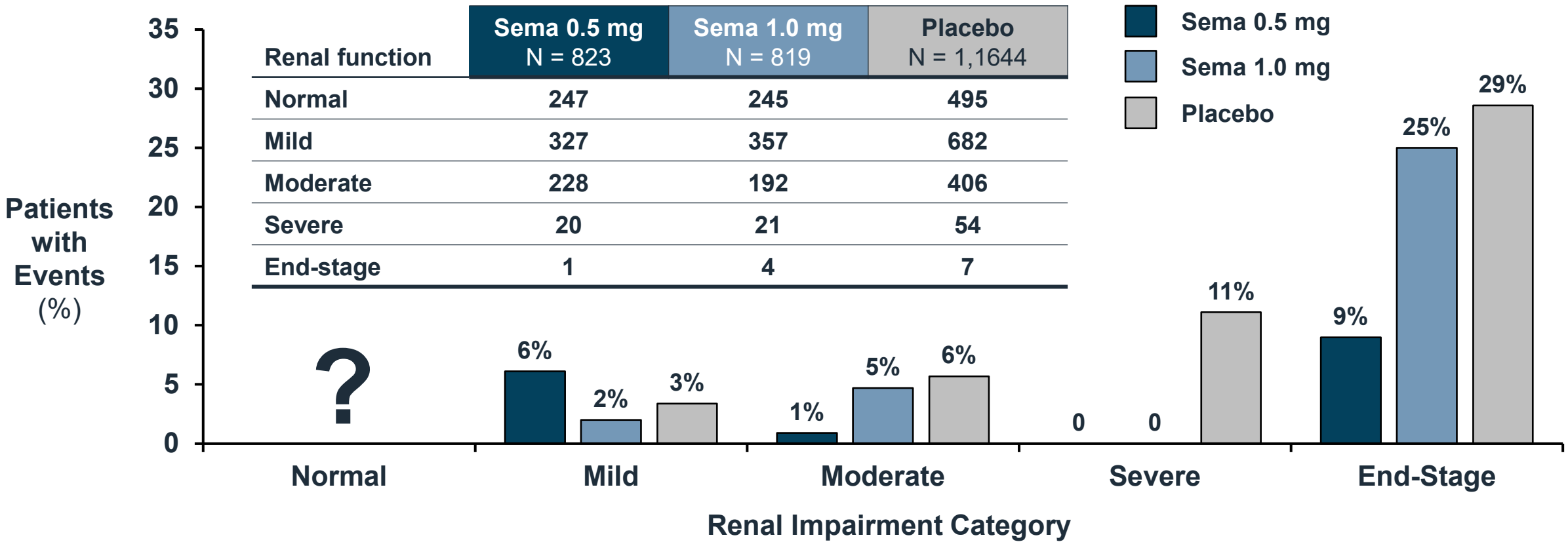
Renal function	Sema 0.5 mg N = 823	Sema 1.0 mg N = 819	Placebo N = 1,1644
Normal	247	819	495
Mild	327	245	682
Moderate	228	357	406
Severe	20	192	54
End-stage	1	21	7



- Figure 67 from FDA's Clinical Review of Semaglutide, addressing Acute Renal Failure
- Where are the AKI data from 987 patients with normal renal function?

SUSTAIN 6: AKI Data in Normal Renal Function is Missing

Renal function	Sema 0.5 mg N = 823	Sema 1.0 mg N = 819	Placebo N = 1,1644
Normal	247	245	495
Mild	327	357	682
Moderate	228	192	406
Severe	20	21	54
End-stage	1	4	7



- ? Where are the data from 987 patients with normal renal function?

SUSTAIN-6: Imputation of Missing AKI Data Shows an AKI Imbalance in Normal Renal Function

Source: NDA 209637 Med Review Fig67 Table185

Renal Function Category	Normal 90+			Mild 60-89			Moderate 30-59			Severe 15-29			ESRF <15		
Category N	987			1366			826			95			12		
Treatment	Sema 0.5	Sema 1.0	Placebo	Sema 0.5	Sema 1.0	Placebo	Sema 0.5	Sema 1.0	Placebo	Sema 0.5	Sema 1.0	Placebo	Sema 0.5	Sema 1.0	Pla
Cohort N	247	245	495	327	357	682	228	192	406	20	21	54	1	4	7
Subjects with ARF Events	11	2	4	20	7	23	2	9	23	0	0	6	0	1	2

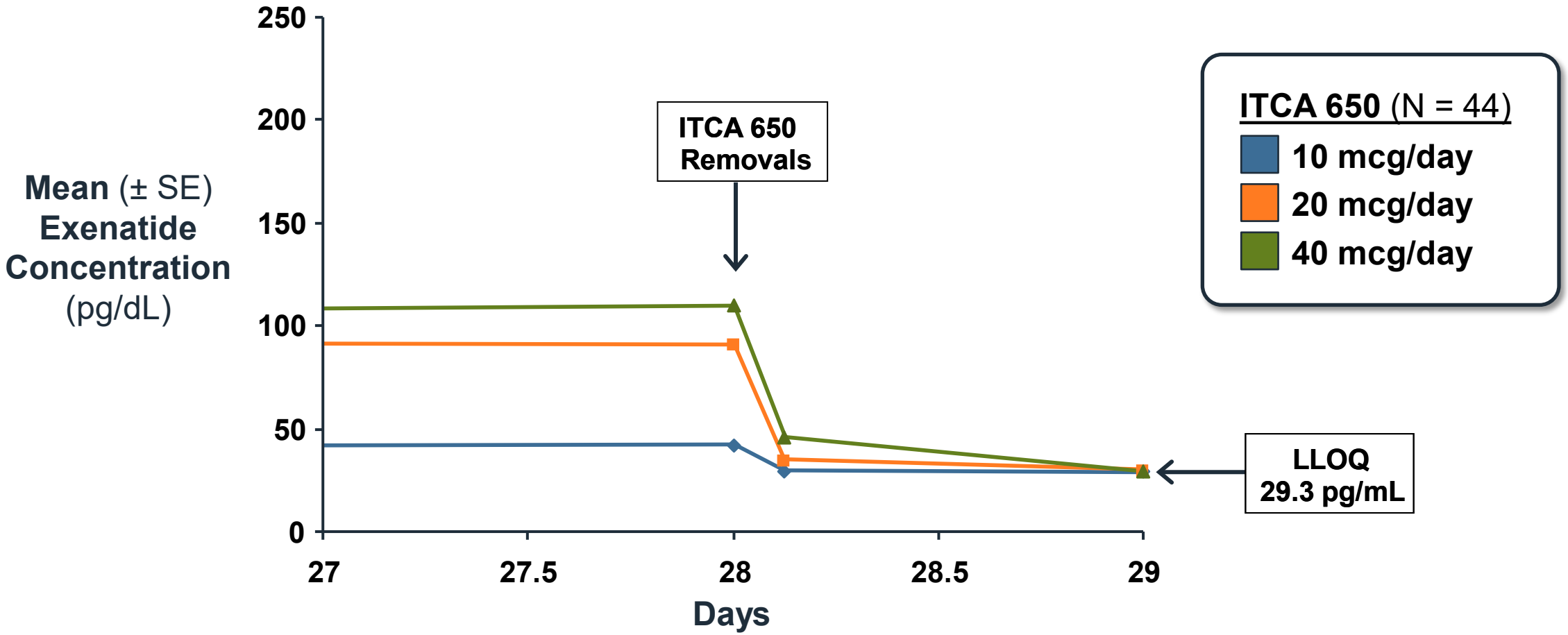
- Omitted values for Normal renal function patients can be imputed (shown in blue) from the adjacent Table 185 in the same document, which shows totals

ITCA 650 has Similar Risk for AKI as GLP-1 Class

	Study 107 CVOT		SUSTAIN-6 0.5 mg CVOT		STEP-2 2.4 mg Non-CVOT		STEP-HFpEF 2.4 mg Non-CVOT	
	ITCA 650 N = 2,075	Placebo N = 2,081	Semaglutide N = 826	Placebo N = 824	Semaglutide N = 403	Placebo N = 402	Semaglutide N = 263	Placebo N = 266
Patients with AKI	11	4	26	18	2*	1**	5	1
Risk	0.5%	0.2%	3.2%	2.2%	0.5%	0.2%	1.9%	0.4%
Estimated Risk ratio	2.76		1.44		2.00		5.06	

*3 total AKI SAEs; 1 repeat case
** pooled placebo

ITCA 650: Once Implants Are Removed Exenatide Levels Decline To Undetectable Levels Within 24 Hours



Study 107: Hypoglycemia Defined in Protocol

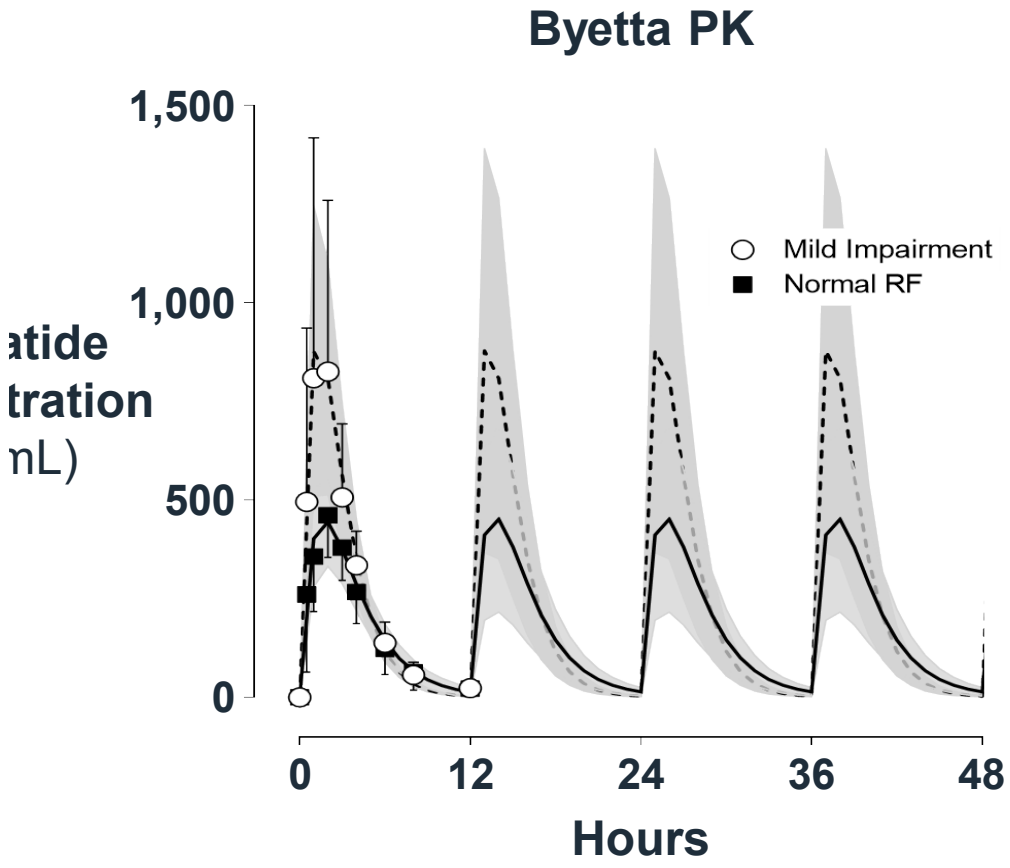
The following definitions relative to hypoglycemia will be used in this study:

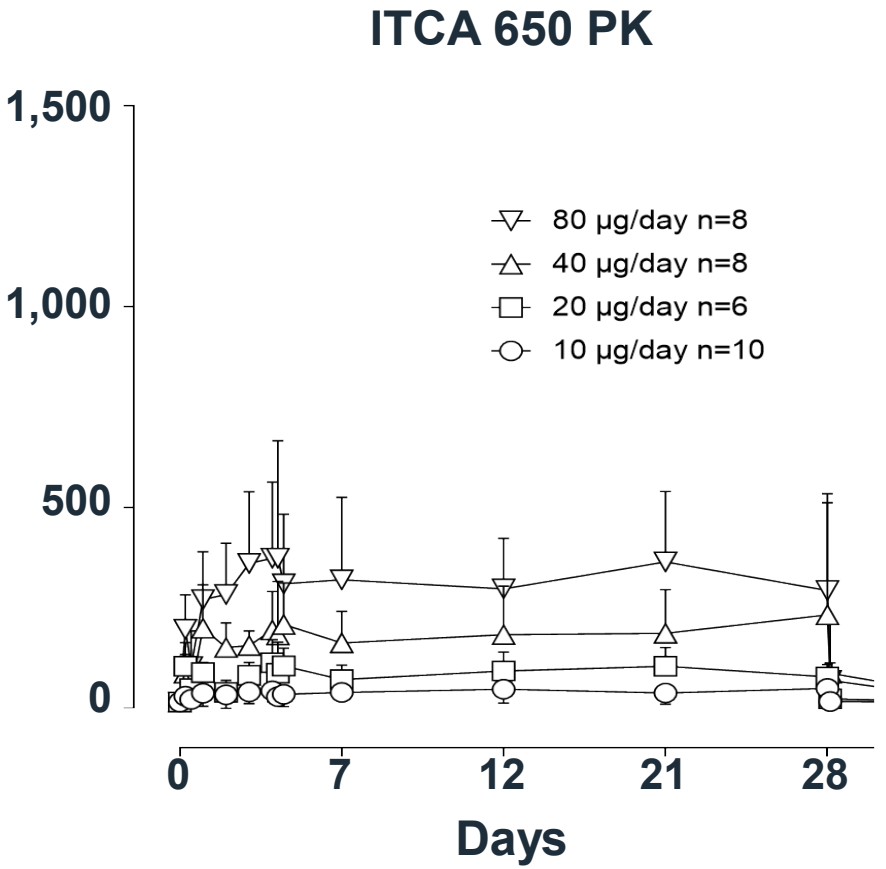
- Confirmed hypoglycemia:
  - Minor hypoglycemia - an event during which symptoms suggestive of hypoglycemia are accompanied by a measured plasma glucose concentration <60 mg/dL (3.3 mmol/L).
  - Major hypoglycemia - an event during which symptoms suggestive of hypoglycemia require the assistance of another person to actively administer carbohydrate, glucagon, or other resuscitative actions. Plasma glucose measurements may not be available during such an event, but neurological recovery attributable to the restoration of plasma glucose to normal is considered sufficient evidence that the event was induced by a low plasma glucose concentration

Meta-Analysis: Cross-Comparisons of Under-Powered Studies are Problematic

Different CVOTS	Patients N	Number of MACE	CV Disease (%)	Median Study Duration (Yrs)	Median Diabetes Duration (Yrs)	Hazard Ratio (95% CI)	Conf Interval Range
Primary ITCA 650 Meta-Analysis	5,151	181	65%	1.2	10	**1.12** (0.83, 1.51)	0.68
Semaglutide: PIONEER-6	3,183	137	85%	1.3	15	**0.79** (0.57, 1.11)	0.54
Semaglutide: SUSTAIN-6	3,297	254	60%	2.1	14	**0.74** (0.58, 0.95)	0.37
Efpeglenatide: Amplitude-0	4,076	314	90%	1.8	15	**0.73** (0.59, 0.93)	0.34
Lixisenatide: ELIXA	6,068	792	100%	2.1	9	**1.02** (0.89, 1.17)	0.28
Liraglutide: LEADER	9,340	1,302	81%	3.8	13	**0.87** (0.78, 0.97)	0.16
Albiglutide: Harmony	9,463	766	100%	1.6	14	**0.78** (0.68, 0.90)	0.22
Dulaglutide: REWIND	9,901	1,257	32%	5.4	10	**0.88** (0.79, 0.99)	0.20
Exenatide QW: EXSCEL	14,752	1,744	73%	3.2	13	**0.91** (0.83, 1.0)	0.17

Exenatide: Byetta PK Data vs ITCA 650 PK Data





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., *et al., Clinical Therapeutics*, 2013.