U.S. FOOD & DRUG ADMINISTRATION

FDA Introductory Remarks

Endocrinologic and Metabolic Drugs

Advisory Committee (EMDAC) Meeting

September 21, 2023

ITCA 650 (exenatide in DUROS)

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Context for Issues to be Discussed

- The Center for Drug Evaluation and Research (CDER) has convened this Advisory Committee (AC) meeting to discuss the new drug application for ITCA 650 (exenatide in DUROS device)
- CDER has determined that this application is not approvable in its current form
- The Applicant requested a public hearing before an AC on CDER's proposal to deny approval of the application
- CDER is holding this AC meeting pursuant to a letter from the FDA Chief Scientist, wherein she granted the Applicant's request for a hearing before an AC

Background

- Type 2 diabetes mellitus (T2DM) is a chronic disease characterized by insulin resistance and progressive loss of β-cell function over time
  - T2DM affects ~37 million Americans
  - Patients are at increased risk of microvascular (i.e., retinopathy, nephropathy, peripheral neuropathy) and macrovascular (i.e., myocardial infarction, stroke) complications
  - Intensive glycemic control, reflected by a reduction in A1C, reduces the incidence of microvascular complications
- Up to half of T2DM patients do not achieve glycemic targets
- Products with benefits beyond glycemic control, fewer adverse reactions, and improved adherence are needed

Members of New Classes of Antihyperglycemic Agents Have Demonstrated Benefits Beyond Glycemic Control

Drug Class	Indications beyond glycemic control in adults with T2DM
Sodium-Glucose Transport 2 Inhibitor (SGLT2)*	To reduce the risk of CV death in adults with T2DM and established CVD (empagliflozin)
	To reduce the risk of HHF in adults with T2DM and either established CVD or multiple CV risk factors (dapagliflozin)
	To reduce the risk of MACE in adults with T2DM and established CVD (canagliflozin)
	To reduce the risk of end-stage kidney disease, doubling of serum creatinine, CV death and HHF in adults with T2DM and diabetic nephropathy with albuminuria (canagliflozin)
Glucagon-like peptide-1 receptor agonist (GLP1RA)	To reduce the risk of MACE in adults with T2DM and established CVD (semaglutide as Ozempic; liraglutide)
	To reduce the risk of MACE in adults with T2DM and established CVD or multiple CV risk factors (dulaglutide)

Source: https://labels.fda.gov

* Some SGLT2i products have additional indications in adults with CKD at risk of progression and in adults with heart failure (with or without T2DM)

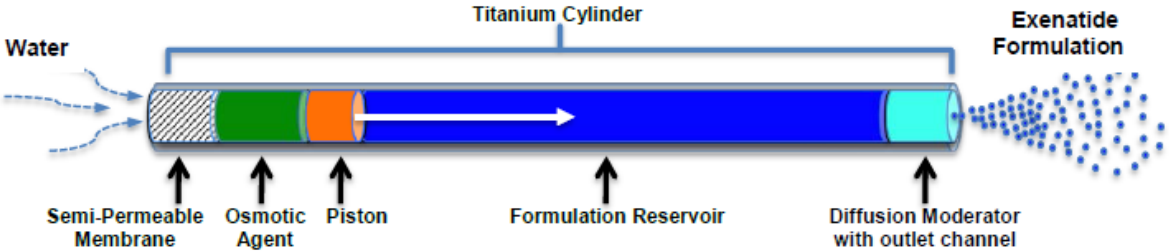
Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; MACE, major adverse cardiovascular event; T2DM, type 2 diabetes mellitus

GLP1 Receptor Agonists (GLP1RAs)

- GLP1RA products are generally characterized by robust effects on A1C
  - GLP1RA products enhance glucose-dependent insulin secretion by the pancreatic beta-cell, suppress inappropriately elevated glucagon secretion, and slow gastric emptying
- Most GLP1RA products approved for glycemic control in patients with T2DM are associated with weight loss
  - GLP-1 is a physiologic regulator of appetite and caloric intake, and the GLP-1 receptor is present in several areas of the brain involved in appetite regulation
  - Some formulations of GLP1RAs (liraglutide as Saxenda; semaglutide as Wegovy) have indications for chronic weight management in obese patients and overweight patients with comorbid conditions
- Cardiovascular outcome trials (CVOTs) of several GLP1RAs have demonstrated reductions in major adverse cardiovascular events (MACE)
  - Although the mechanisms of blood glucose lowering and weight loss are better understood, the mechanism(s) responsible for observed CV benefits have not been fully elucidated

ITCA 650 (Exenatide in DUROS)

- ITCA 650 is a drug-device combination product:
  - Subdermal implantable device with a mini-osmotic pump
  - Contains a different exenatide formulation from the formulations approved as Byetta and Bydureon
- The proposed dosing regimen is:
  - A device stated to deliver 20 mcg/day of exenatide for 3 months
  - Followed by titration to a device stated to deliver 60 mcg/day of exenatide for 6 months



Source: NDA 209053 (Seq. 0059), Description and Composition of the Drug Product, Module 3.2.P.1, p. 3.

GLP1RA Products Approved to Improve Glycemic Control in Adults with T2DM

Product	Approval Date	Dosing Regimen	Non-glycemic Indications in Adults - Approval Date
Byetta (exenatide IR)	4/28/2005	Twice daily injection	
Victoza (liraglutide)	1/25/2010	Once daily injection	To reduce the risk of MACE in adults with T2DM and established CVD – 8/25/2017
Bydureon (exenatide ER)	1/27/2012	**Once weekly injection**	
Tanzeum (albiglutide)*	4/15/2014	Once weekly injection	
Trulicity (dulaglutide)	9/18/2014	**Once weekly injection**	To reduce the risk of MACE in adults with T2DM and established CVD or multiple CV risk factors – 2/21/2020
Adlyxin (lixisenatide)*	7/27/2016	Once daily injection	
Ozempic (semaglutide injection)	12/5/2017	**Once weekly injection**	To reduce the risk of MACE in adults with T2DM and established CVD – 1/16/2020
Rybelsus (semaglutide oral tablet)	9/20/2019	**Once daily oral**	

Source: Drugs@FDA: FDA Approved Drug Products, available at http://www.accessdata.fda.gov/scripts/cder/daf/.

* No longer marketed in the United States.

Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; GLP1RA, glucagon-like peptide-1 receptor agonist; MACE, major adverse cardiovascular event; T2DM, type 2 diabetes mellitus; IR, immediate release; ER, extended release

ITCA 650 - Top Line CDER Findings

- In vitro studies:
  - Release of exenatide inconsistent, fluctuating between under-delivery and over-delivery
- Pharmacokinetic data:
  - Very limited, but consistent with in vitro studies
  - Observed exposures were variable and showed occasional sudden large increases
- Efficacy:
  - Treatment effect is an approximate 0.7% reduction in A1C (versus placebo)
- Clinical safety:
  - Unfavorable imbalances observed in acute kidney injury (AKI) events, MACE events, overall serious adverse events, and all-cause mortality
    - Most serious AKI events were preceded by gastrointestinal events
    - Meta-analysis of the MACE events from all GLP1RA CVOTs suggests that the ITCA 650 CVOT is an outlier

CDER Position

- The device issues, along with the finding of variable PK with rapid fluctuations, and the available clinical safety data raise uncertainty about the benefit-risk assessment of ITCA 650
- The safety signals associated with ITCA 650 should be addressed via submission of additional premarket data
- Patient adherence is a critical clinical issue. However, the potential for improved adherence among patients who might prefer biannual medical procedures versus once weekly self-administered injections needs to be balanced against any additional risks
- Overall, the benefit-risk assessment for the product is unfavorable based on the available data

Charge to the Committee

Discussion Question #1

Discuss your assessment of the safety profile of ITCA 650 and whether the safety profile of the ITCA 650 drug-device combination product has been adequately characterized based on available data:

a. with respect to acute kidney injury
b. with respect to cardiovascular safety
c. with respect to overall safety

Discussion Question #2

Discuss your assessment of the benefit risk balance of ITCA 650 for the indication to improve glycemic control in patients with type 2 diabetes mellitus (T2DM).

Voting Question

VOTE: Based on the available data has the Applicant demonstrated that the benefits of the ITCA 650 drug-device combination product outweigh its risks for the treatment of T2DM?

a. If yes, explain your rationale.
b. If no, explain your rationale and comment on additional data that could be provided to demonstrate the benefits outweigh the risks.

ITCA 650 (exenatide in DUROS)
Device Review Conclusions

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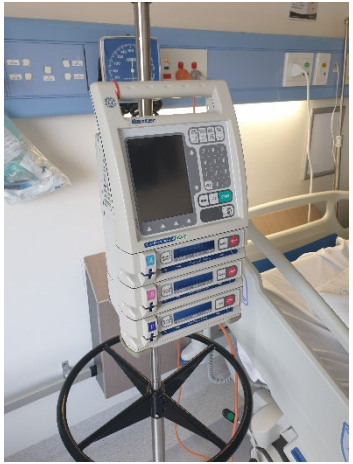
Office of Product Evaluation and Quality (OPEQ)
Center for Devices and Radiological Health (CDRH)

Considerations for Drug Delivery Devices in Combination Products

- Deliver the intended dose of a specified drug
- Common delivery devices include prefilled syringes, pen injectors, autoinjectors, on-body infusion devices, (implanted) infusion pumps, etc.

- When selecting a delivery system, some important considerations to ensure safety and efficacy are:
  - If the delivery performance of the device is adequate to achieve the intended therapeutic effect.
  - If the device is compatible with the intended therapeutic
  - That the device design meets patient/user needs

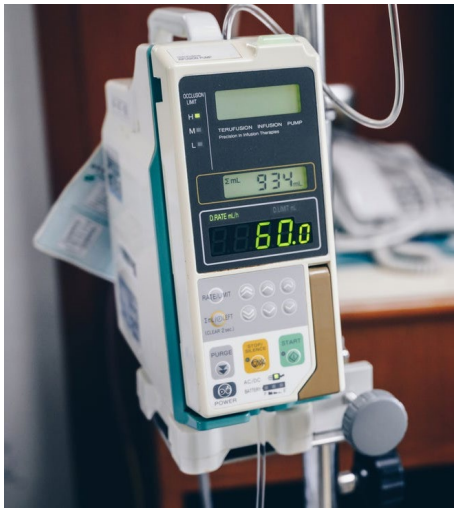


https://www.unitedinfusion.com/collections/baxter-iv-pumps
Anaphylaxis - Knowledge @ AMBOSS
SmartDose® 3.5 On-Body Drug Delivery Systems (OBDS) (westpharma.com)

Considerations for Infusion Devices in Combination Products

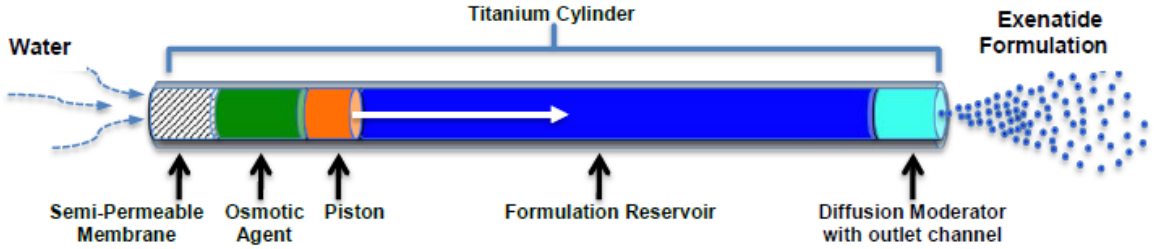
Infusion Products:

- Intended to deliver drug at a specified rate
- Infusion rate accuracy requirements are based on the clinical acceptability of the intended drug
- Can be operated at different flow rates commonly with an accuracy of ±5-15%
- Fault conditions are typically detected and communicated to the end user via alarms



Insulin Pump Therapy | Medtronic Diabetes Israel (medtronic-diabetes.com)
CDRH 2022 Annual Report (fda.gov)

ITCA 650 – Exenatide in DUROS Device



- ITCA 650 is a drug-device combination product consisting of an exenatide drug suspension and an osmotic mini-pump. The product is proposed in a 20 mcg/day (3 months initiation dose) and 60 mcg/day (6 months maintenance dose) presentation
- The device was previously approved for use with leuprolide (VIADUR)
- The ITCA 650 exenatide formulation consists of a viscous, anhydrous suspension of spray-dried exenatide powder with markedly higher viscosity compared to the dimethyl sulfoxide-based solution of Viadur
- The device does not have a means to communicate the delivery status to the patient or healthcare provider (e.g., Bluetooth, NFC, wireless)

NFC: Near field communication

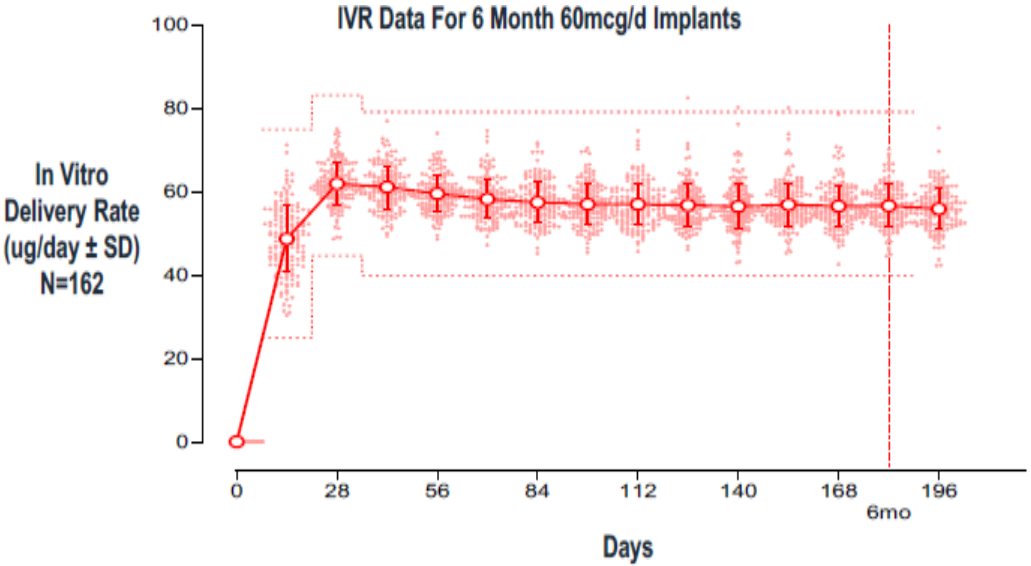
Source: NDA 209053 (Seq. 0059), Description and Composition of the Drug Product, Module 3.2.P.1, p. 3.

Assessing Drug Delivery Performance of ITCA 650

- The DUROS device is intended to provide consistent release of drug to the patient over the duration of use

- The Applicant developed an *in-vitro* assay to evaluate the delivery performance of the device. The In-Vitro Release (IVR) test is done under controlled conditions by placing the ends of the device in phosphate buffered saline or a release medium. At different timepoints, aliquots are taken and exenatide is quantified

- Initially, weekly (20 mcg/day) or biweekly (60 mcg/day) sampling data were provided



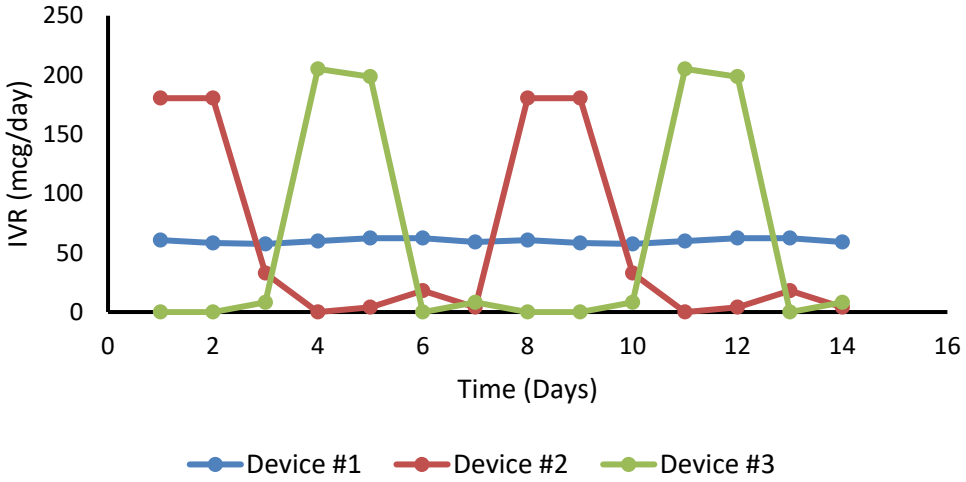
Source: Intarcia Briefing Document pg. 113

Weekly or Biweekly Sampling Does Not Test a Clinically Relevant Delivery Interval

Infrequent sampling can mask device inaccuracies and day-to-day performance:

- Excessively long sampling intervals can mask significant variabilities in the drug delivery rate
- The half-life of exenatide is about 2 to 4 hours
- Daily sampling was requested based on clinical use and feasibility.

Hypothetical devices each delivering 840 mcg over two weeks



Each of these hypothetical devices delivers 840 mcg (60 mcg x 14 days) of drug over the 2-week period.

Proposed Daily IVR Acceptance Criteria Lack Clinical Justification

- Common delivery accuracies of drug delivery devices:
  - Injection devices: ±5% (i.e., 95% - 105% of the intended dose)
  - Infusion devices: ±5 - 15%
- Specifications should be set so that devices delivering drug at the extremes of the specifications are still safe and effective
- The proposed daily IVR Acceptance Criteria allow for variations of up to 3.3 - 200% of the intended dose and lack clinical justification

Dosage Target	Timepoint	Proposed IVR Range
20 mcg/day	Week 1 (0 to 7 days)	2-40 mcg/day
	Week 2 (7 to 14 days)	2-40 mcg/day
	Weeks 3 to 13 (14 to 91 days)	10-36 mcg/day
60 mcg/day	Weeks 1 to 2 (0 to 14 days)	2-120 mcg/day
	Weeks 3 to 4 (14 to 28 days)	2-120 mcg/day
	Weeks 5 to 26 (28 to 182 days)	25-110 mcg/day

Source: CDER Reviewer's summary, adapted from Study VV 52888 (SDN0060), Table 3 and Table 4.

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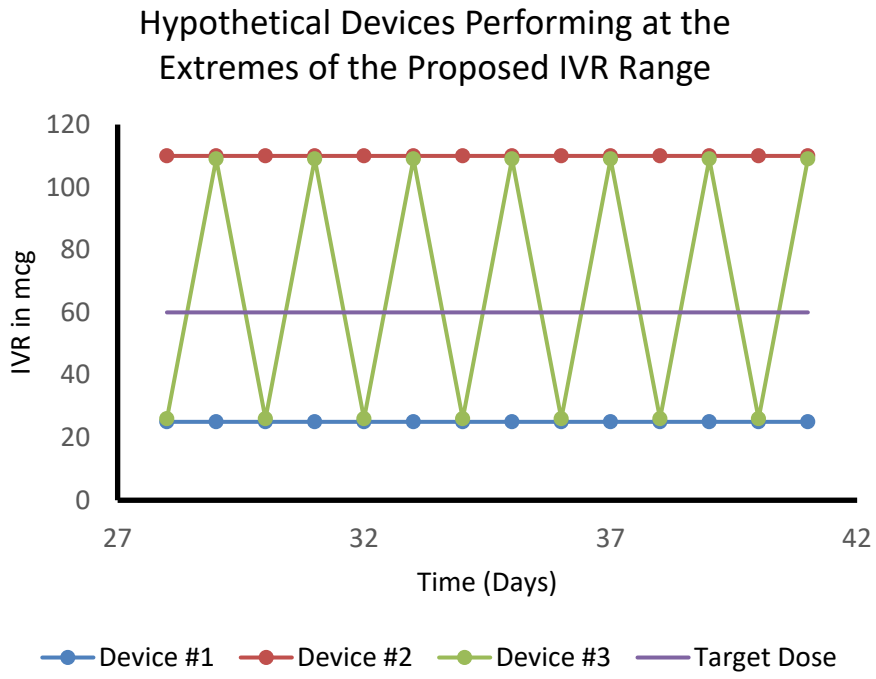
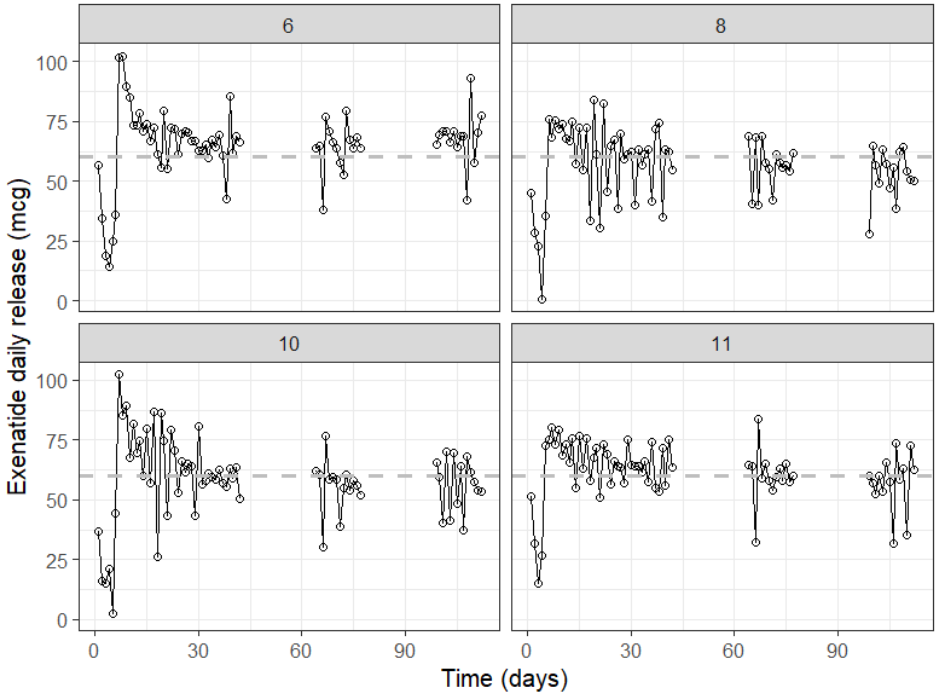


Daily IVR Data Shows Significant Day-to-Day Variability

- Daily IVR data shows day-to-day variability in both 20 mcg/day and 60 mcg/day presentations
- While variations are observed in all tested devices, some exhibited significantly more IVR variability
- The highest IVR variations are observed within the first 1-3 weeks of use
- Out of the 12 devices in Group B, 2 deviated from the proposed acceptance criteria

Daily In Vitro Release Data From ITCA 650 60 mcg/Day Devices (Units 6B, 8B, 10B, 11B) – Group B (Daily Data Collected During Select Intervals, Days 0-112)

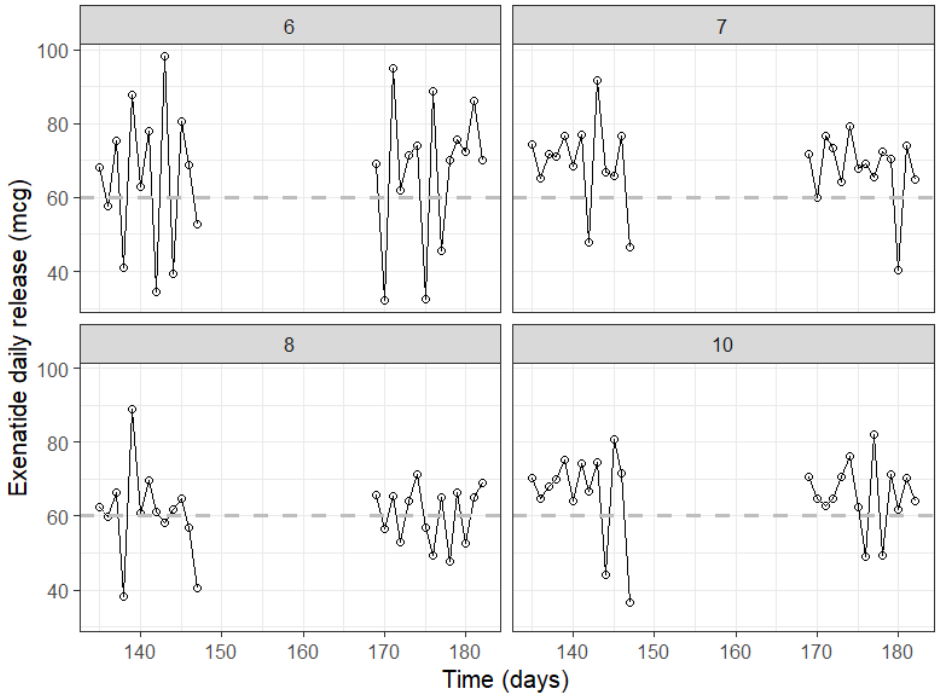


Note: weekly average measurements and transfer measurements are omitted

Daily IVR Data Shows Significant Day-to-Day Variability

- Variable daily IVR can be observed throughout the intended use life of the implant
- Outside of the initial 1-3 weeks of delivery, some devices from Group C (112 – 182 days) showed the highest day-to-day variability

Daily In Vitro Release Data From ITCA 650 60 mcg/Day Devices (Units 6C, 7C, 8C, 10C) – Group C (Daily Data Collected During Select Intervals, Days 112-182)



Note: weekly average measurements and transfer measurements are omitted

Daily IVR Specification

Figure 34: ITCA 650 60 mcg/day Implants - Upper and Lower Limits IVR Specifications

FDA Misinterpreted IVR Specification

FDA Interval	Daily Range (mcg)	% of 60 mcg Target Range
0-28 Days	2 – 120	3 – 200%
28-182 Days	25 - 110	42 – 183%

Intarcia IVR Specification

Intarcia Interval	Daily Range (mcg)	% of 60 mcg Target Range
0-14 Days	30 – 70	50 – 117%
14-28 Days	51 – 77	85 – 125%
28-42 Days	46 – 73	76 – 122%
70-84 Days	46 – 73	
126-140 Days	46 – 73	
168-182 Days	46 – 73	

Left: Adapted from Study VV 52888 (SDN0060); Right: Not found in NDA, provided in Applicant AC background materials

In the Applicant's background material, new daily IVR specifications were proposed that appear to be based on weekly/biweekly specifications

Daily IVR Specification

Assessment of Daily IVR Data Based on Proposed Specification

IVR Interval	Daily IVR Range (mcg)	Number of Devices that meet Specifications
0-14 Days	30 – 70	0/12
14-28 Days	51 – 77	4/12
28-42 Days	46 – 73	3/12
70-84 Days	46 – 73	7/12
126-140 Days	46 – 73	7/12
168-182 Days	46 – 73	3/12

When analyzing the existing daily IVR data against the newly proposed specifications, each tested device experienced Out-of-Specification (OOS) events with a combined total of 200 OOS events (approximately 20%) for the 60 mcg/day devices

Device Performance and Reliability Are Not Acceptable for the Intended Use

- Failure modes are mechanisms by which the device can fail. The Applicant has not adequately defined and investigated the failure of the ITCA 650 device
  - E.g., the failure mode “inconsistent formulation delivery” was defined as three instances where the weekly IVR rate is ≥ 50% the target rate
  - Any deviations from clinically validated specifications should be categorized as a failure. Hence, this definition can significantly underestimate the number of devices that experienced this failure mode

- Even though daily IVR acceptance criteria were set wide, some devices still failed to meet them
  - E.g., Unit 3B delivered 0 and 1 mcg on days 2 and 3 which both deviate from the acceptance criteria. Similarly, Unit 11A and 3B failed to meet the acceptance criteria

Overall Device Review Conclusions

1. Drug delivery is highly variable and remains inconsistent throughout the intended use period
2. Weekly/Biweekly average sampling rates mask the significant day-to-day variability observed in the daily IVR study
3. The proposed upper and lower delivery limits allow for significant variability and lack clinical justification
4. Device failures are more frequent than typical for drug delivery devices and users would not be able to detect a failure

Clinical Pharmacology Assessment of ITCA 650

Edwin Chiu Yuen Chow, Ph.D.
Clinical Pharmacology Team Leader
Division of Cardiometabolic and Endocrine Pharmacology
Office of Clinical Pharmacology

PK Evaluation of In Vivo Drug Release Performance of ITCA 650

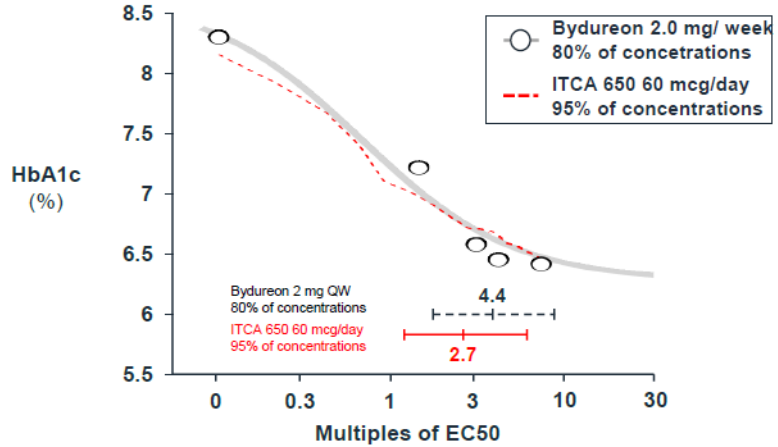
Methodologies used for comparison between exenatide products

Applicant	CDER
• Exposure-response analysis (A1C changes) • Analysis focused on drug concentrations of a population (e.g., mean-level) • Emphasis on longer-term drug clearance changes (month to month)	• Analysis focused on drug concentrations within an individual (e.g., subject-level) • Emphasis on short term drug concentrations changes (hour to hour, day to day)

PK = pharmacokinetics

A1C Response Is Not a Sensitive Metric to Capture the Impact of Sudden Excursions in Concentrations

Figure 41: Exenatide PK/PD Profiles: Exposure Response Data Modeled for ITCA 650 vs Bydureon Show ITCA 650 Exposure is Less Variable / Not Higher



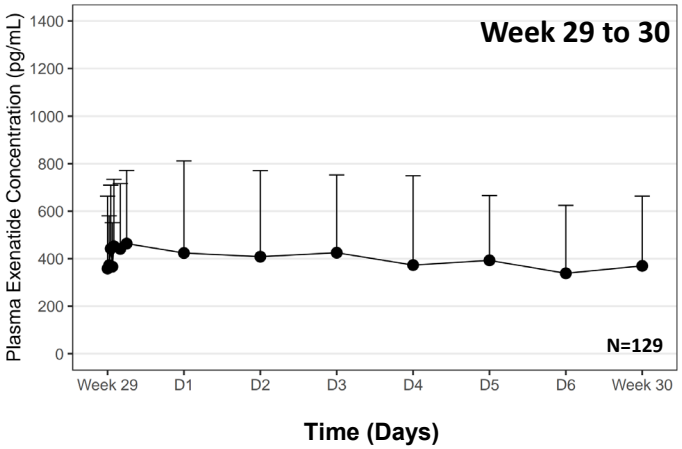
Source: Applicant's Briefing Document, Page 124

- These graphs show population averages (PK) and do not represent sudden excursions in concentrations
- The main concern is not the efficacy; A1C is not a sensitive measure for evaluating the within subject variability
- There is no established exposure-response model for safety

Mean Concentration-Time Profile of Exenatide Products Does Not Describe Within Subject Variability (WSV)

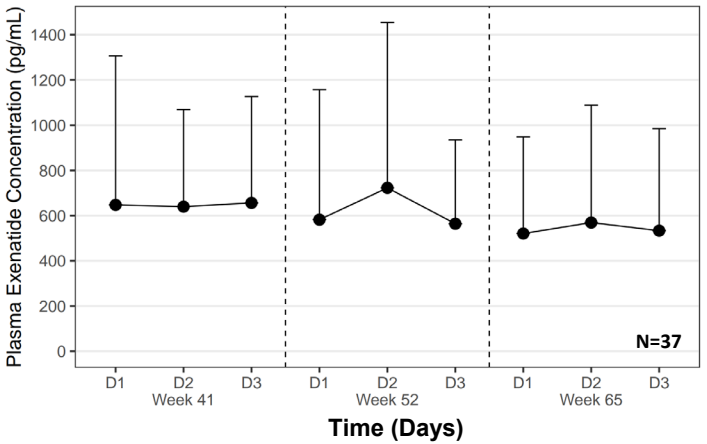
Bydureon[1]: 2 mg Once Weekly

Study LAR-105



ITCA 650[2]: 60 µg/Day

Study CLP-103SS



- We cannot infer day-to-day fluctuations within the same subject from such mean-level data
- Error bars represent + 1 Standard Deviation (SD) of the population data. This variability is a combination of between-subject and within-subject variability

Source:

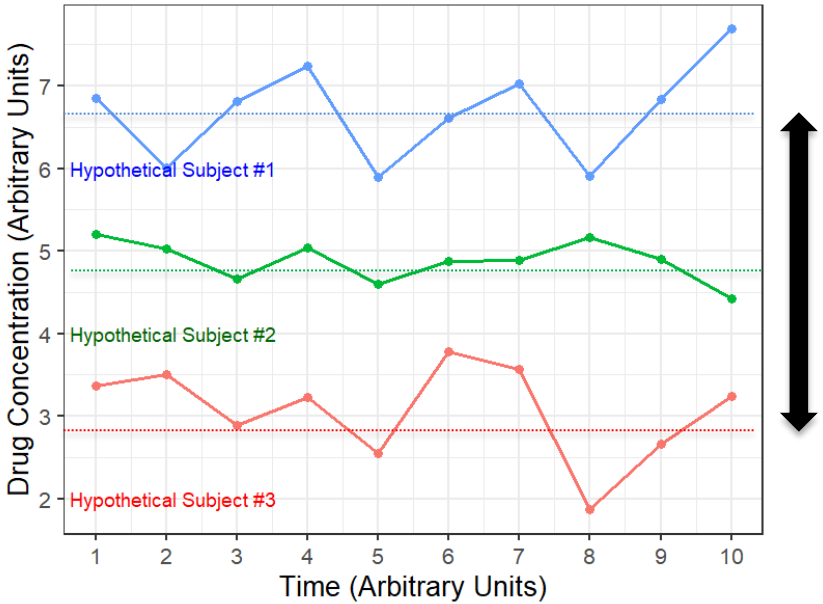
[1]https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000ClinPharmR.pdf; Figure 10; Data modified using arithmetic mean and standard deviation

[2] CDER Review Staff; data represented arithmetic mean and standard deviation

Within-subject and Between-subject Variabilities are Different Pharmacokinetic Concepts

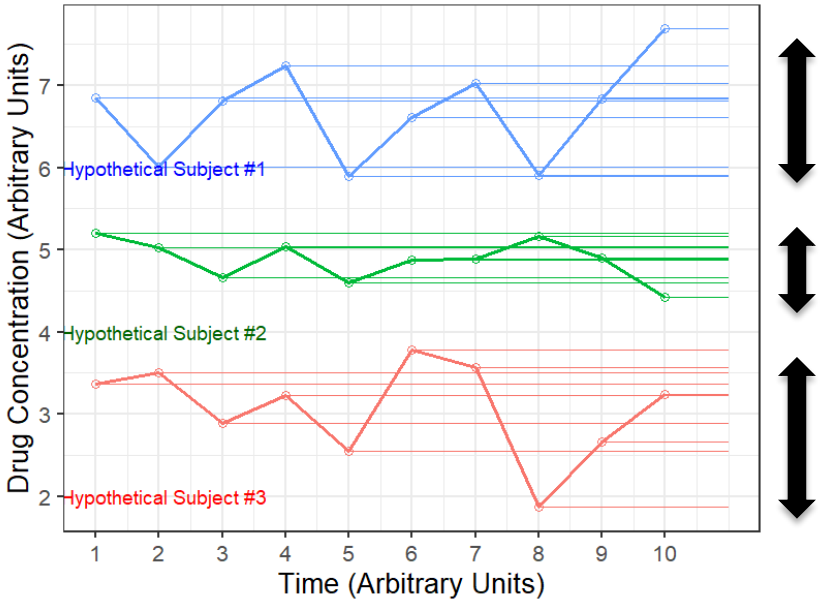
Between-subject variability (BSV)

- Spread of average drug concentrations among different subjects
  - **Intrinsic Factors:** Body weight, race, age, organ function etc.



Within-subject variability (WSV)

- Spread of drug concentrations (within the same subject) among different time
  - **Formulation Factors:** Drug release



Clinical Studies with PK Information Used in the Assessment of PK Variability

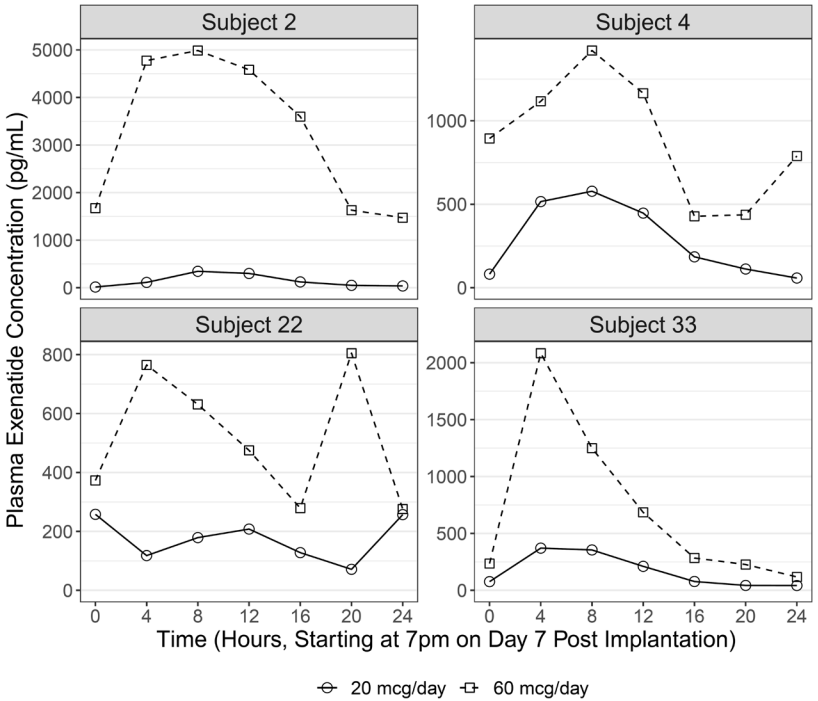
Study	Description	N	PK sampling	Device Used	Device Lot
CLP-01	Phase 1 dose escalation	38	By day	20, 40, 80 µg/day	Group A
CLP-02	Phase 2 24-week dose ranging study	141	By week	20, 40, 60 µg/day	Group A
CLP-103SS	Phase 3 substudy extension of Study 103	37	By day & week	60 µg/day	Group B
CLP-109	Renal impairment study	38	By hour	20, 40, 60 µg/day	Group B
CLP-115	Drug-drug interaction study with drug cocktail	33	By hour	20, 60 µg/day	Group B
CLP-116	Drug-drug interaction study with oral combination contraceptive	27	By hour	20, 60 µg/day	Group B

Source: CDER Review Staff

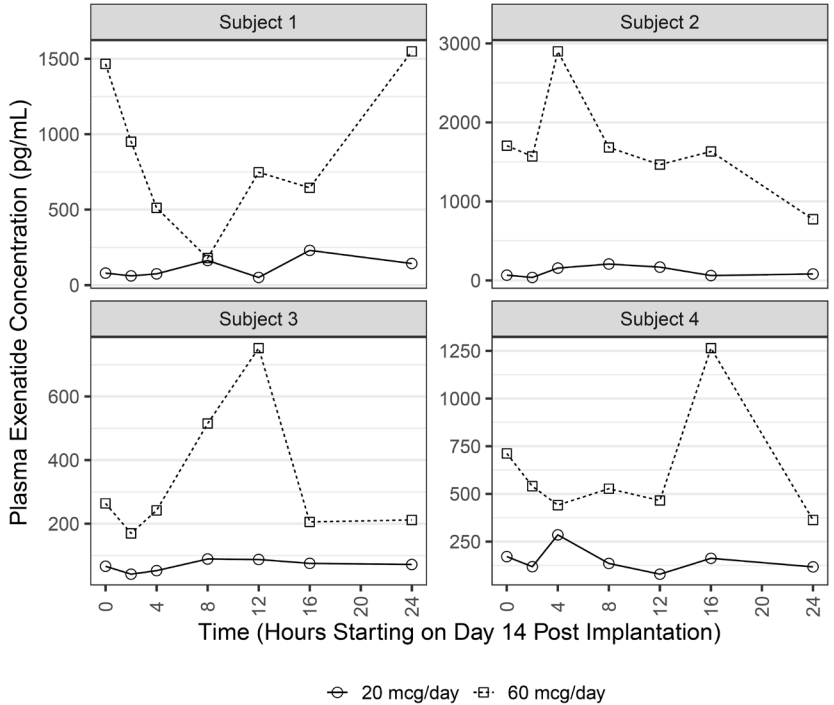
- PK data in Study CLP-01 and CLP-02 are not informative as a different lot and PK assay were used
- Study CLP-115 was not used as PK data are not at steady state
- PK data were collected for 37 subjects after completion of primary analyses (CLP-103SS)

Exenatide Within-Day Variability of ITCA 650 at Steady State

Study CLP-109 (4/38 PK profiles)



Study CLP-116 (4/27 PK profiles)



Source: CDER Review Staff

Exenatide Within-Day Variability of ITCA 650 at Steady State

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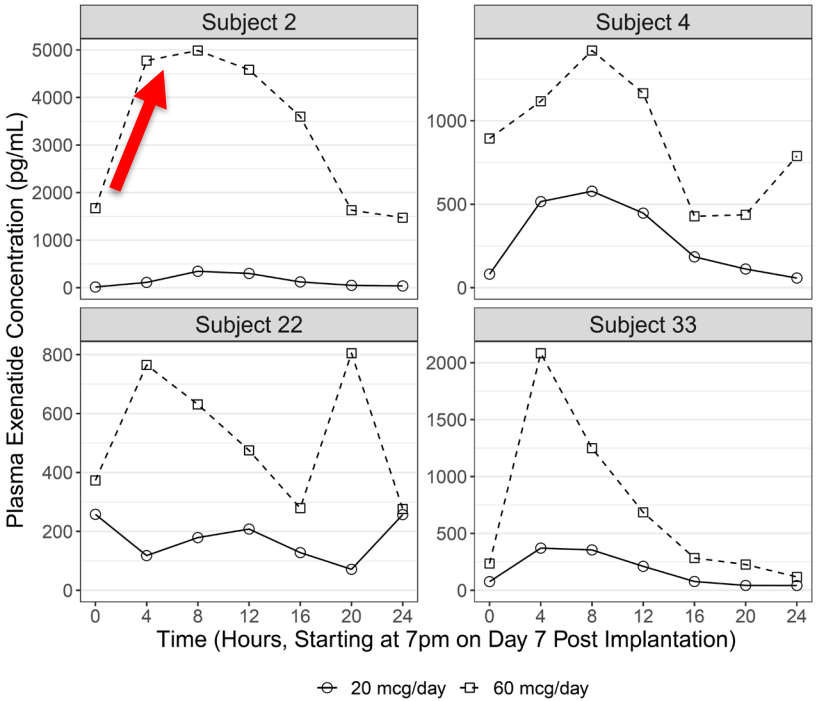

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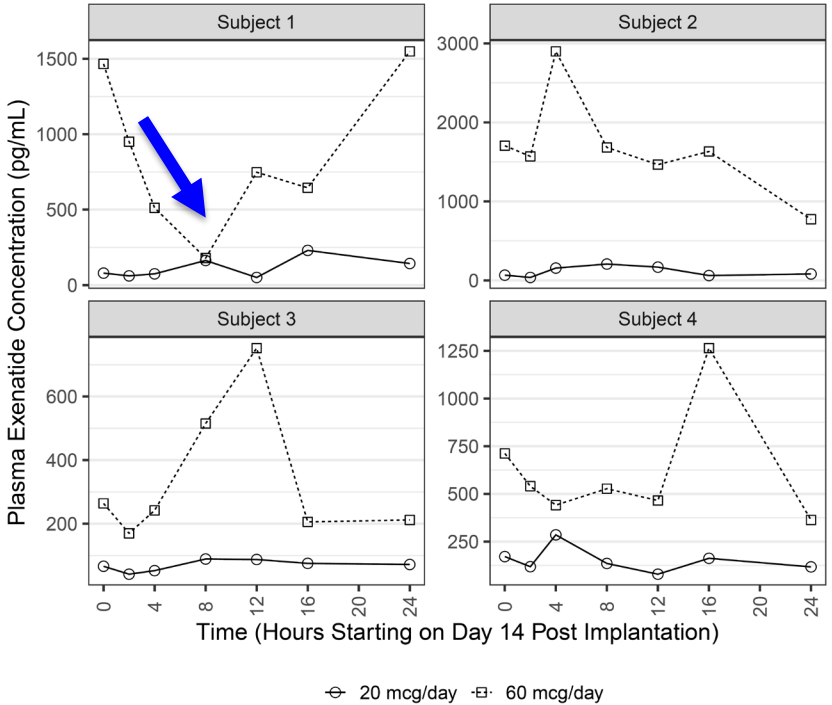
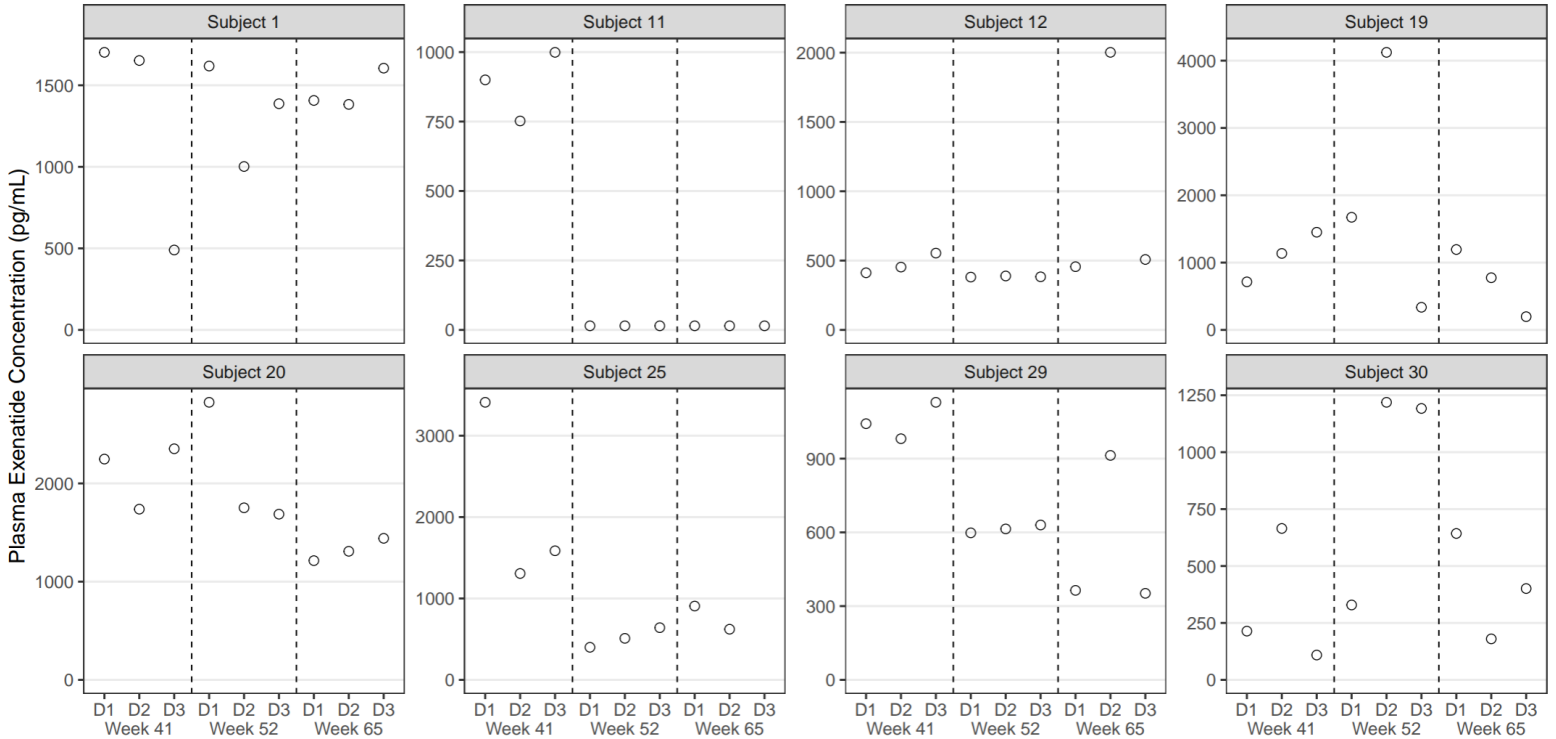


Source: CDER Review Staff

Exenatide Between Days and Between Weeks Variability of ITCA 650 at Steady State

Study CLP-103SS (8/37 PK Profiles)

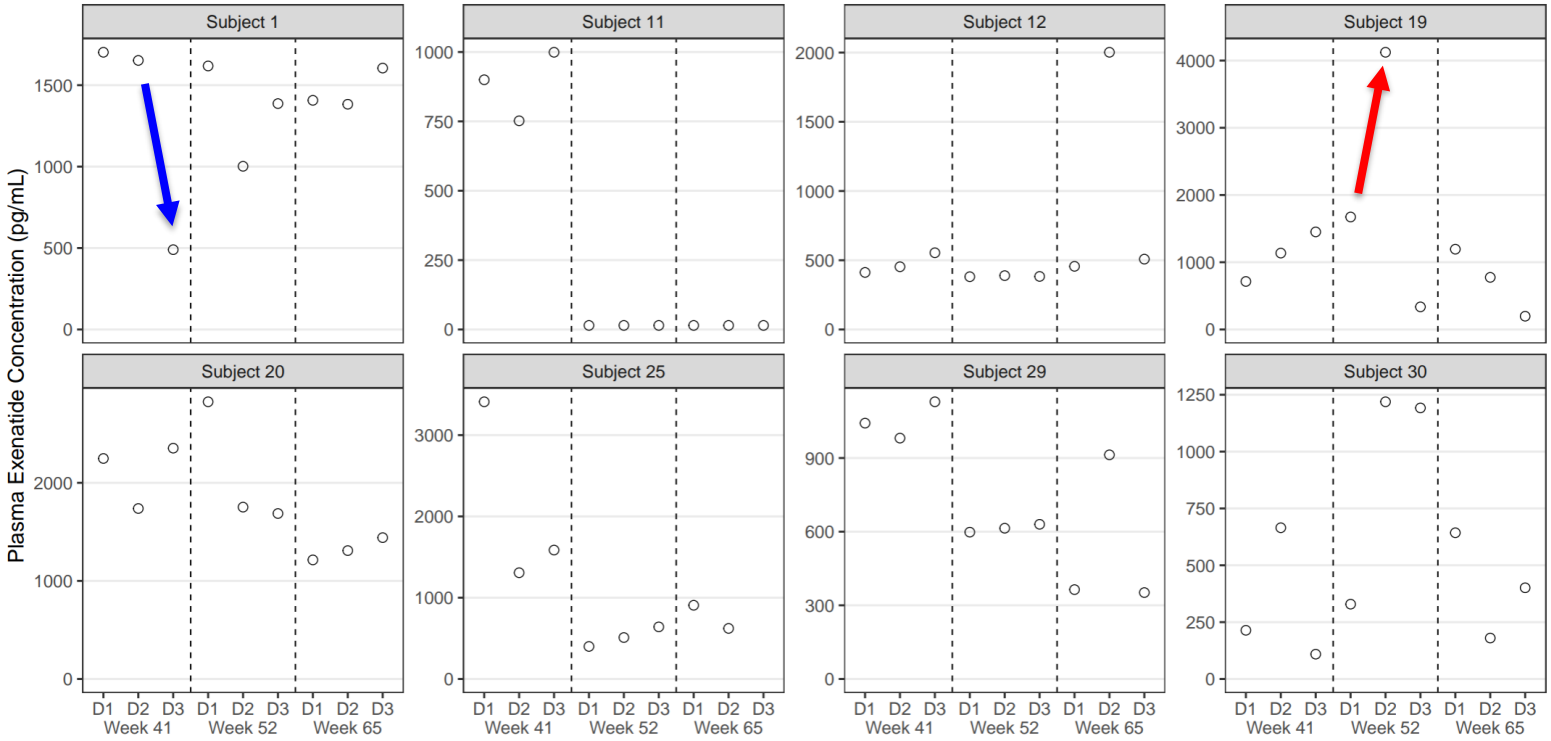


Note that for Subject 11, there was a device malfunction on Weeks 52 and 65

Source: CDER Review Staff

Exenatide Between Days and Between Weeks Variability of ITCA 650 at Steady State

Study CLP-103SS (8/37 PK Profiles)



Note that for Subject 11, there was a device malfunction on Weeks 52 and 65

Source: CDER Review Staff

Month-to-Month Variability in Exenatide Clearance Is Not the Appropriate Measure of Within-Day and Between-Day Variability in Concentrations

Variability Parameter	ITCA 650
Early release upon placement or injection	Yes
Within-subject CV	
Average Css over 24 hours	38%[a]
Individual concentrations over 24 hours	65%[b]
Between-subject CV	
Average Css	48%, 67%[c]
Individual concentrations	70%[e]
Variability from the population PK model	
Within-subject	29%
Between-subject	41%

Source: Applicant's Briefing Document, Page 120

This value represents month-to-month variability on exenatide clearance

This value does not capture the within-day or the day-to-day variability in concentrations within a subject, due to sudden excursion or inconsistent drug release.

Within-Day and Between-Day Variability in Concentrations Is More Appropriate to Capture Isolated Changes in Concentrations

Variability Parameter	ITCA 650
Early release upon placement or injection	Yes
Within-subject CV	
Average Css over 24 hours	38%[a]
Individual concentrations over 24 hours	65%[b]
Between-subject CV	
Average Css	48%, 67%[c]
Individual concentrations	70%[e]
Variability from the population PK model	
Within-subject	29%
Between-subject	41%

Source: Applicant's Briefing Document, Page 120

CDER considers this a better approach to describe within-subject variability (WSV) and to capture changes in concentrations within a day or between days.

This value represents month-to-month variability on exenatide clearance

This value does not capture the within-day or the day-to-day variability in concentrations within a subject, due to sudden excursion or inconsistent drug release.

Within-Day and Between-Day WSV for ITCA 650 and Bydureon

Within Subject Variability (WSV)	ITCA 650 (Study CLP-103SS)	ITCA 650 (Study CLP-109)	Bydureon (Study 104)	Bydureon (Study 105)
Within-day	NA	**66%**	20%	21%
Between-day	**42%**	**68%**	32%	30%

Source: CDER Review Staff

- **Within-day WSV:** variability in concentrations collected within 24 hours in each subject, expressed as %CV (coefficient of variation)
- **Between-day WSV:** variability in concentrations collected across different days in each subject, expressed as %CV (coefficient of variation)

Clinical Pharmacology Summary

- Average trends from exposure-response, specifically for A1C, are not a sensitive metric to capture sudden excursions in concentrations

- Mean drug concentration time profiles may mask fluctuation in concentration over time within the same subject

- In vivo individual level PK data for ITCA 650 show inconsistent exenatide release with marked excursions in some subjects, happening hour-to-hour, day-to-day and week-to-week

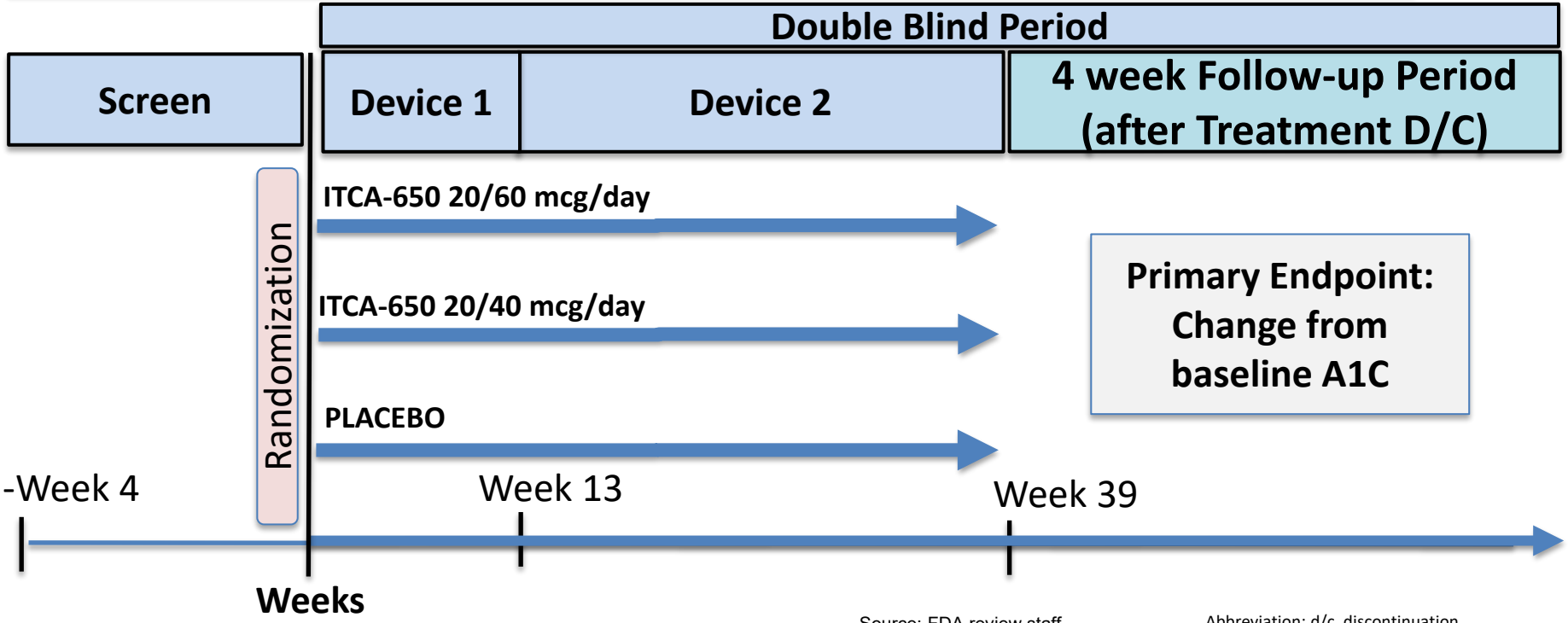
- ITCA 650 product showed a higher within day and between day within-subject variability as compared to Bydureon

OVERVIEW OF SOURCES OF CLINICAL DATA FOR EFFICACY AND SAFETY

PATRICK ARCHDEACON, MD

Study CLP-103

Inclusion criteria: Adults w/ T2DM ≥3 months; A1C ≥7.5% and ≤10% on stable regimen of diet, exercise ± Met/SU/TZD
US Only (126 sites)



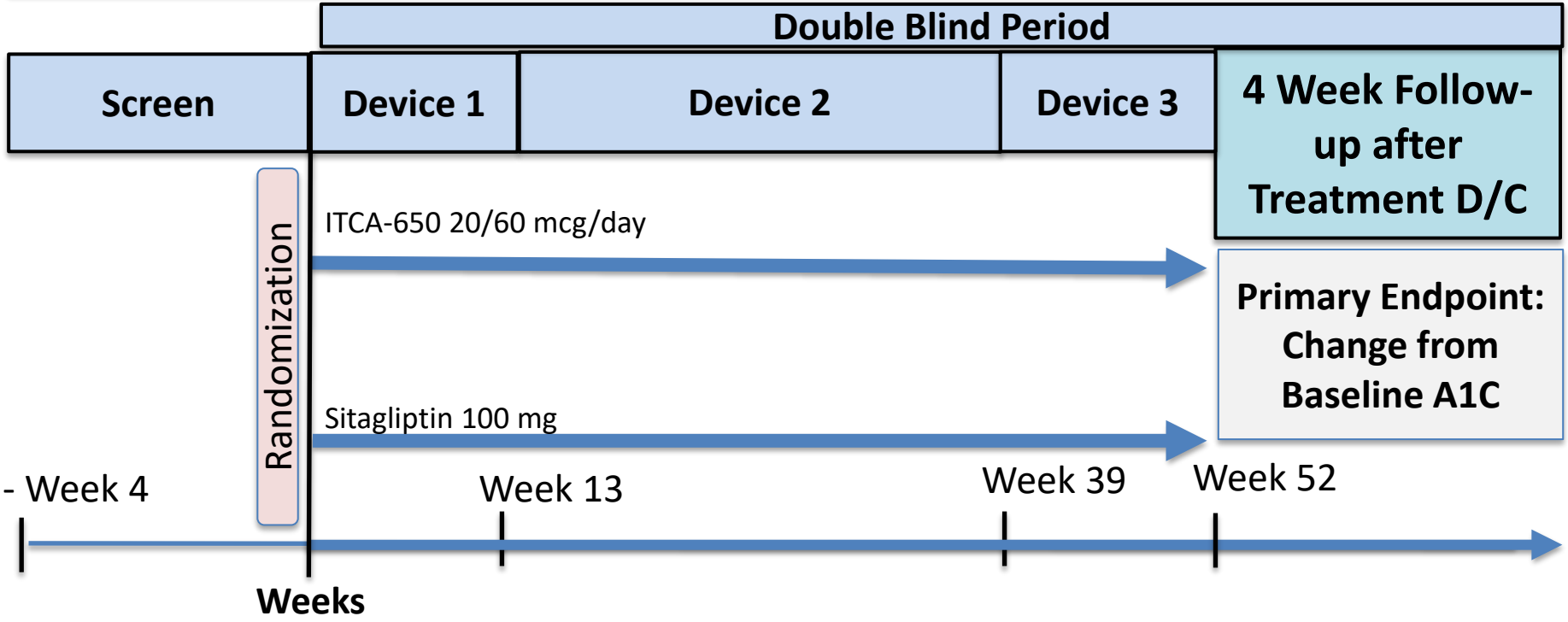
Source: FDA review staff

Abbreviation: d/c, discontinuation

Study CLP-105

Inclusion criteria: Adults w/ T2DM ≥3 months; A1C ≥7.5% and ≤10% on stable regimen of ≥1500 mg metformin daily

124 sites in 13 countries

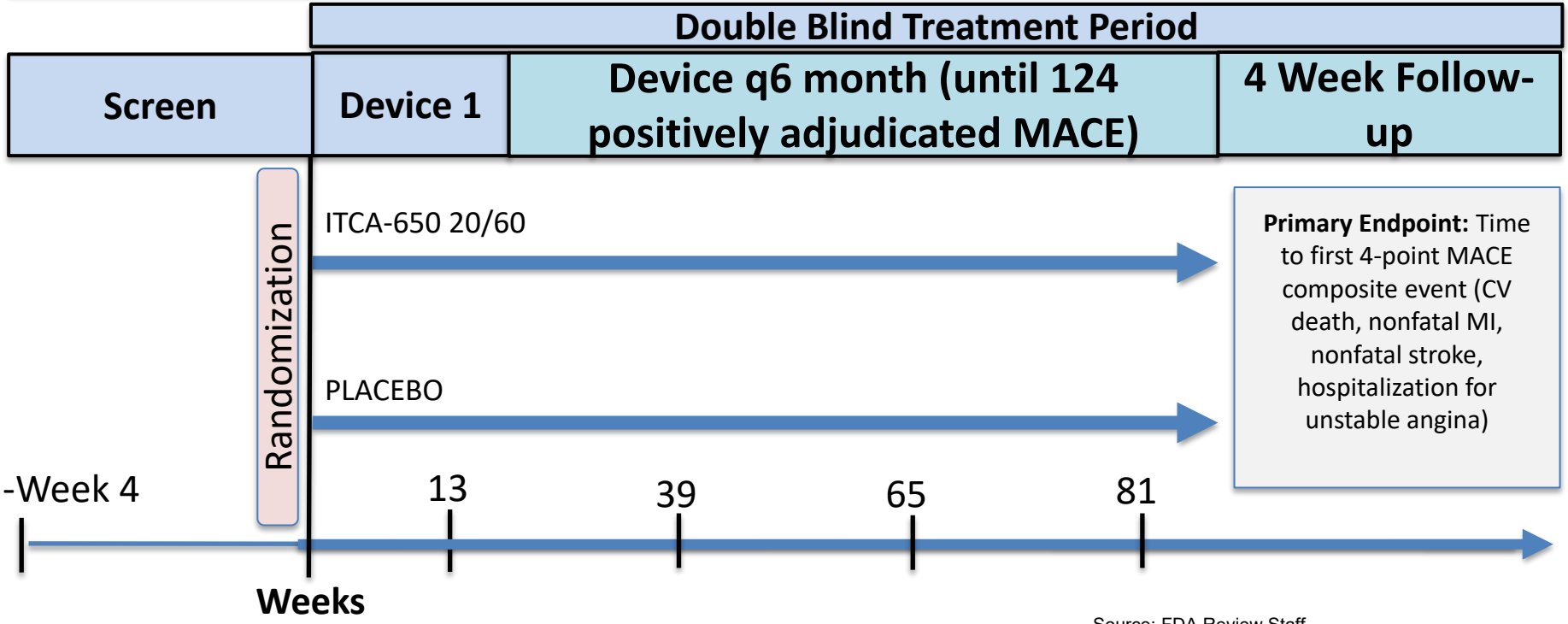


Source: FDA review staff

Abbreviation: D/C, discontinuation

Study CLP-107 (FREEDOM)

Inclusion criteria: Adults w/ T2DM ≥3 months; A1C ≥6.5% and "high" CV risk (established CV disease) or "low" CV risk (multiple CV risk factors)
402 sites in 27 countries



Source: FDA Review Staff

Demographics of Core Clinical Trials

	CLP-103 N=460	CLP-105 N=535	CLP-107 (CVOT) N=4156
Male (%)	59	57	63
Hispanic or Latino (%)	35	43	28
Asian (%)	1	4	1
Black (%)	14	12	5
White (%)	83	77	92
Median Age, years [IQR]	55 [48, 62]	56 [48, 61]	63 [57, 68]
Age <50 (%)	28	28	7
Age 50-<65 (%)	56	56	54
Age 65-<75 (%)	15	14	33
Age ≥75 (%)	2	2	7

Source: CDER Review staff. Analysis: R v. 4.2. using ADaM (adsl.xpt) from SDN0000. ITT population.

Subject Characteristics in Core Clinical Trials (1)

	CLP-103 N=460	CLP-105 N=535	CLP-107 (CVOT) N=4156
Median A1C %	8.4	8.4	8.0
[IQR]	[7.8, 9.1]	[7.8, 9.3]	[7.2, 9.3]
Antidiabetic drug use			
Metformin	392 (85)	530 (99)	3526 (86)
Sulfonylurea	217 (47)	1 (0.2)	1850 (44.5)
TZD	14 (3.0)	0 (0.0)	84 (2.0)
Insulin	0 (0.0)	0 (0.0)	1474 (35.5)
Diabetes duration			
<5 years	145 (31.5)	177 (33.1)	834 (20.1)
5-10 years	146 (31.7)	184 (34.4)	1136 (27.3)
>10 years	169 (36.7)	174 (32.5)	2186 (52.6)

Source: CDER Review staff. Analysis: R v. 4.2. using ADaM (adsl.xpt) from SDN0000. ITT population.

Subject Characteristics in Core Clinical Trials (2)

	CLP-103 N=460	CLP-105 N=535	CLP-107 (CVOT) N=4156
History of MI	17 (3.7)	13 (2.4)	1070 (25.7)
History of Revascularization	11 (2.4)	11 (2.1)	922 (22.2)
History of CVA	6 (1.3)	7 (1.3)	470 (11.3)
History of PAD	12 (2.6)	10 (1.9)	957 (23.0)
History of CHF	0 (0.0)	8 (1.5)	568 (13.7)
Statin use	205 (44.6)	186 (34.8)	2794 (67.2)
Antiplatelet use	149 (32.4)	114 (21.3)	3050 (73.4)
Aspirin use	146 (31.7)	107 (20.0)	2462 (59.2)
ACE-Inhibitor use	213 (46.3)	232 (43.4)	2199 (52.9)
ARB Use	57 (12.4)	65 (12.1)	998 (24.0)
Baseline diuretic use	61 (13.3)	95 (17.8)	1289 (31.0)

MI: Myocardial infarction; CVA: Cerebrovascular accident: PAD: peripheral artery disease; CHF: Congestive heart failure

Source: CDER Review staff. Analysis: R v. 4.2. using ADaM (adsl.xpt) from SDN0000. ITT population.

Most Subjects in Core Clinical Trials Had Baseline eGFR >60 mL/min/1.73m^2

	CLP-103	CLP-105	CLP-107 (CVOT)
	N=460	N=535	N=4156
Median eGFR mL/min/1.73m^2	85	86	80
[IQR]	[74, 99]	[75, 98]	[68, 93]
eGFR category (%)			
Normal (≥90 mL/min/1.73m^2)	189 (41.1)	228 (42.6)	1243 (29.9)
Mild (60-89 mL/min/1.73m^2)	270 (58.7)	282 (52.7)	2501 (60.2)
Moderate (30-59 mL/min/1.73m^2)	1 (0.2)	25 (4.7)	408 (9.8)
Severe (15-29 mL/min/1.73m^2)	0 (0.0)	0 (0.0)	3 (0.1)
Urine albumin/creatinine ratio			
<30 mcg/mg	NR	NR	2733 (65.8)
≥30-≤300 mcg/mg	NR	NR	1139 (27.4)
>300 mcg/mg	NR	NR	280 (6.7)

Source: CDER Review staff. Analysis: R v. 4.2. using ADaM (adsl.xpt) from SDN0000. ITT population.

NR - not recorded

Baseline Characteristics Across GLP1RA CVOTs

	Trials in Patients with or at risk of CVD								Trial in Patients post-ACS
	EXSCEL[1] Exenatide N=14,752	AMPLITUDE-0[2] Efpeglenatide N=4076	LEADER[3] Liraglutide N=9340	SUSTAIN-6[4] Semaglutide N=3297	PIONEER-6[5] Semaglutide N=3183	REWIND[6] Dulaglutide N=9901	HARMONY[7] Albiglutide N=9463	FREEDOM[8] Exenatide N=4156	ELIXA[9] Lixisenatide N=6068
Median duration (years)	3.2	1.8	3.8	2.1	1.3	5.4	1.6	1.4	2.1
Established CVD (%)	73	90	81	83	85	32	100	76	100
Age (years)	62	65	64	65	66	66	64	62	60
A1C (%)	8.1	8.9	8.7	8.7	8.2	7.3	8.7	8.3	7.7
Diabetes duration (years)	13	15	13	14	15	10	14	11	9
BMI (kg/m^2)	32	33	33	33	32	32	32	33	30
eGFR ≥90 mL/min/1.73m^2 (%)	29	NR	35	30	29	27	30	30	23
eGFR 60-89 mL/min/1.73m^2 (%)	49	NR	42	42	44	51	47	60	53
eGFR <60 mL/min/1.73m^2 (%)	22	31	23	29	27	23	23	10	23

[1]Holman et al. (2017), [2]Gerstein et al. (2021),[3]Marso et al. (2016a),[4]Marso et al. (2016b), [5]Husain et al. (2019),[6]Gerstein et al. (2019),[7]Hernandez et al. (2018),[8]Ruff et al. (2022),[9]Pfeffer et al. (2015)

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide-1 receptor agonist; A1C, hemoglobin A1C; HR, hazard ratio; MACE, major adverse cardiovascular event; NR, not reported

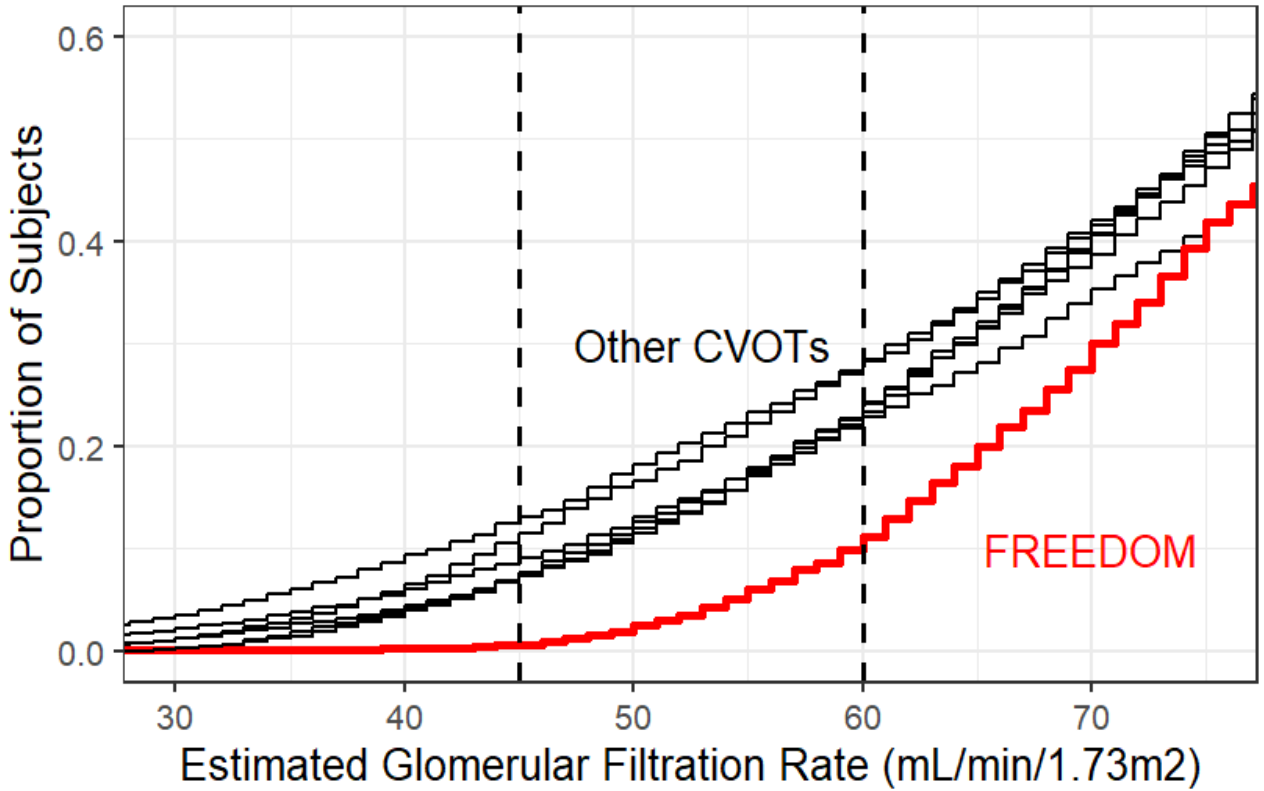
Baseline Characteristics Across GLP1RA CVOTs

	Trials in Patients with or at risk of CVD								Trial in Patients post-ACS
	EXSCEL[1] Exenatide N=14,752	AMPLITUDE-0[2] Efpeglenatide N=4076	LEADER[3] Liraglutide N=9340	SUSTAIN-6[4] Semaglutide N=3297	PIONEER-6[5] Semaglutide N=3183	REWIND[6] Dulaglutide N=9901	HARMONY[7] Albiglutide N=9463	FREEDOM[8] Exenatide N=4156	ELIXA[9] Lixisenatide N=6068
Median duration (years)	3.2	1.8	3.8	2.1	1.3	5.4	1.6	1.4	2.1
Established CVD (%)	73	90	81	83	85	32	100	76	100
Age (years)	62	65	64	65	66	66	64	62	60
A1C (%)	8.1	8.9	8.7	8.7	8.2	7.3	8.7	8.3	7.7
Diabetes duration (years)	13	15	13	14	15	10	14	11	9
BMI (kg/m^2)	32	33	33	33	32	32	32	33	30
eGFR ≥90 mL/min/1.73m^2 (%)	29	NR	35	30	29	27	30	30	23
eGFR 60-89 mL/min/1.73m^2 (%)	49	NR	42	42	44	51	47	60	53
eGFR <60 mL/min/1.73m^2 (%)	22	31	23	29	27	23	23	10	23

[1]Holman et al. (2017), [2]Gerstein et al. (2021),[3]Marso et al. (2016a),[4]Marso et al. (2016b), [5]Husain et al. (2019),[6]Gerstein et al. (2019),[7]Hernandez et al. (2018),[8]Ruff et al. (2022),[9]Pfeffer et al. (2015)

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide-1 receptor agonist; A1C, hemoglobin A1c; HR, hazard ratio; MACE, major adverse cardiovascular event; NR, not reported

Proportion of Subjects with Impaired eGFR Was Lower in FREEDOM Than Other GLP1RA CVOTs



Source: CDER Review staff; software: R v. 4.2; Data: adsl.xpt (SDN0000) and subject listings from other CVOTs

Subject Disposition-Study CLP-103

Parameter	ITCA 650 20/40 mcg/day	ITCA 650 20/60 mcg/day	Placebo
Randomized and treated (%)	153 (100.0)	153 (100.0)	154 (100.0)
Received glycemic rescue (%)	26 (17.0)	18 (11.8)	65 (42.2)
Completed the study On-Treatment (%)	120 (78.4)	123 (80.4)	123 (79.9)
Prematurely discontinued treatment (%)	33 (21.6)	30 (19.6)	31 (20.1)
Adverse Event	18 (11.8)	12 (7.8)	5 (3.2)
Loss of glycemic control	0 (0.0)	1 (0.7)	2 (1.3)
Loss to follow-up	1 (0.7)	0 (0.0)	3 (1.9)
Other	2 (1.3)	4 (2.6)	5 (3.2)
Pregnancy	0 (0.0)	1 (0.7)	1 (0.6)
Withdrawal by subject	12 (7.8)	12 (7.8)	15 (9.7)
Completed follow-up visit (%)	140 (91.5)	141 (92.2)	139 (90.3)

Source: Source: CDER Review staff. Analysis: R v. 4.2 using ADaM (adsl.xpt) from SDN0000. ITT population.

Subject Disposition-Study CLP-105

Parameter	ITCA 650 20/60 mcg/day	Sitagliptin 100 mg/day
Randomized (%)	268 (100.0)	267 (100.0)
Randomized and treated (%)	265 (98.9)	265 (99.3%)
Received glycemic rescue (%)	40 (14.9)	97 (36.3)
Completed the treatment (%)	204 (76.1)	217 (81.3)
Prematurely discontinued treatment (%)	64 (23.9)	50 (18.7)
Adverse Event	31 (11.6)	10 (3.7)
Loss of glycemic control	3 (1.1)	4 (1.5)
Loss to follow-up	3 (1.1)	2 (0.7)
Other	9 (3.4)	11 (4.1)
Withdrawal by subject	18 (6.7)	21 (7.9)
Completed follow-up visit (%)	248 (92.5)	247 (92.5)

Safety population

Source: CDER Review staff. Analysis: R v. 4.2 using ADaM (adsl.xpt) from SDN0000.
ITT population.

Subject Disposition- FREEDOM

Parameter	ITCA 650 20/60 mcg/day	PLACEBO
Randomized (%)	2075 (100.0)	2081 (100.0)
End of study status (%)		
Known alive	2012 (97.0)	2022 (97.2)
Known deceased	49 (2.4)	41 (2.0)
Unknown	14 (0.7)	18 (0.9)
Completed study On-Treatment (%)	1705 (82.2)	1786 (85.8)
Discontinued treatment prematurely (%)	370 (17.8)	295 (14.2)
Any adverse event	258 (12.4)	104 (5.0)
Withdrawal by subject	68 (3.3)	124 (6.0)
Other	44 (2.1)	67 (3.2)
Completed study (%)	1996 (96.2)	2007 (96.4)
Discontinued study (%)	79 (3.8)	74 (3.6)
Adverse event	47 (2.3)	39 (1.9)
Loss to follow-up	15 (0.7)	13 (0.6)
Other	6 (0.3)	7 (0.3)
Withdrawal by subject	11 (0.5)	15 (0.7)

includes loss of glycemic control, loss to follow up, excluded medication

Source: CDER Review staff. Analysis: R v. 4.2 using ADaM (adsl.xpt) from SDN0000.

EFFICACY REVIEW OF STUDIES CLP-103 AND CLP-105

Wenda Tu, PhD, Statistical Reviewer
Division of Biometrics II (DBII)
Office of Biostatistics (OB)

Outline

- Summary of Studies
- Key Efficacy Endpoints
- Primary Analysis Methods
- Key Efficacy Results
- Conclusion

Summary of Studies

Study CLP-103	Study CLP-105
Phase 3, multicenter, randomized, parallel-design, double-blind, **placebo-controlled, superiority trial**	Phase 3, multicenter, randomized, parallel-design, double-blind, **active-controlled, non-inferiority (NI) trial (NI margin = 0.3%) ****
• ITCA 650 20/40 mcg/day (N = 153*) • ITCA 650 20/60 mcg/day (N = 153) • Placebo (N = 154)	• ITCA 650 20/60 mcg/day (N = 265) • Sitagliptin 100 mg/day (N= 265)

* N = randomized and treated subjects

** Superiority to sitagliptin would be tested as the first key secondary hypothesis if non-inferiority was successfully demonstrated.

Key Efficacy Endpoints

	Study CLP-103*	Study CLP-105**
Primary	Change from baseline in A1C (%) at Week 39	Change from baseline in A1C (%) at Week 52
Key Secondary	Change from baseline in body weight (kg) at Week 39	Incidence of A1C reduction > 0.5% and weight loss ≥ 2kg at Week 52
	Incidence of A1C < 7% at Week 39	Change from baseline in body weight (kg) at Week 52
		Incidence of A1C < 7% at Week 52

* The Type 1 error was controlled by a serial gatekeeper strategy, with alpha (overall two-sided alpha =0.05) split evenly between the high and low dose sequences.

** The Type 1 error (overall two-sided alpha =0.05) was controlled by a serial gatekeeper strategy.

Applicant's Primary Analysis Method

	Study CLP-103	Study CLP-105
Analysis set	Randomized and treated subjects with valid baseline and at least one-post baseline A1C data.	
Analysis model	ANCOVA[1]	MMRM[2]
Missing data handling	LOCF	Imputation by MAR
Visit window definition	Study visits were labelled by visit numbers, regardless of the actual visit days (i.e., 1st visit → Study Visit 1, 2nd visit → Study Visit 2…)	

ANCOVA = Analysis of Covariance, MMRM = mixed model repeated measures, LOCF = last observation carried forward, MAR = missing at random

1. The ANCOVA model adjusted for treatment groups, sulfonylurea use (Yes / No), and baseline A1C.
2. The MMRM analysis adjusted for treatment groups, visit, and treatment-by-visit interactions, and baseline A1C

CDER Reviewer's Analysis Method

	Study CLP-103	Study CLP-105
Analysis set	Randomized and treated subjects	
Analysis model	ANCOVA[1]	ANCOVA[2]
Missing data handling	Multiple imputation based on return to baseline[3]	
Visit window definition	± 25 days (3.5 weeks) of the scheduled visit days[4]	

ANCOVA = Analysis of Covariance

1. This ANCOVA model adjusted for treatment groups, sulfonylurea use (Yes / No), and baseline A1C (same as the Applicant's).
2. This ANCOVA model adjusted for treatment groups and baseline A1C.
3. Wang Y et al., 2023
4. Since visits were generally scheduled 7 weeks apart, the 3.5-week window size ensures no overlapping windows, and that data could be classified with the closest visit at which they were recorded.

Primary Efficacy Result, CLP-103

A1C (%) Change from Baseline at Week 39

		ITCA 650 20/40 mcg/day	ITCA 650 20/60 mcg/day	Placebo
Applicant's Analysis	N	147	151	143
	Baseline, Mean (SD)	8.5 (0.8)	8.4 (0.8)	8.5 (0.8)
	Change at Week 39 (SE)	-1.0 (0.1)	-1.1 (0.1)	-0.1 (0.1)
	Difference from placebo (97.5% CI)	-1.0 (-1.3, -0.7)	-1.1 (-1.4, -0.8)	
	Missing A1C Data at Week 39, n (%)	32 (21%)	28 (18%)	30 (19%)
CDER Reviewer's Analysis	N	153	153	154
	Baseline, Mean (SD)	8.5 (0.8)	8.4 (0.8)	8.5 (0.8)
	Change at Week 39 (SE)	-1.0 (0.1)	-1.1 (0.1)	-0.3 (0.1)
	Difference from placebo (97.5% CI)	-0.7 (-1.0, -0.4)	-0.7 (-1.0, -0.4)	
	Missing A1C Data at Week 39, n (%)	34 (22%)	29 (19%)	34 (22%)

* For both the Applicant's and CDER's analyses, p-value (two-sided) < .001 for both high dose and low dose vs placebo.

Primary Efficacy Result, CLP-105

A1C (%) Change from Baseline at Week 52

		ITCA 650 20/60 mcg/day	sitagliptin 100 mcg/day
Applicant's Analysis	N	263	257
	Baseline, Mean (SD)	8.5 (0.9)	8.7 (0.9)
	Change at Week 52 (SE)	-1.5 (0.1)	-0.8 (0.1)
	Difference from sitagliptin (95% CI)	-0.7 (-0.9, -0.5)	
	Missing A1C Data at Week 52, n (%)	62 (23%)	47 (18%)
CDER Reviewer's Analysis	N	265	265
	Baseline, Mean (SD)	8.5 (0.9)	8.7 (0.9)
	Change at Week 52 (SE)	-1.3 (0.1)	-0.9 (0.1)
	Difference from sitagliptin (95% CI)	-0.4 (-0.6, -0.2)	
	Missing A1C Data at Week 52, n (%)	62 (23%)	49 (18%)

* For both the Applicant's and CDER's analyses, p-value (two-sided, superiority test) < .001.

Efficacy Result on Body Weight, CLP-103

Body Weight (kg) Change from Baseline at Week 39

		ITCA 650 20/40 mcg/day	ITCA 650 20/60 mcg/day	Placebo
Applicant's Analysis	N	147	151	143
	Baseline, Mean (SD)	96.7 (18.5)	97.7 (18.3)	97.3 (21.6)
	Change at Week 39 (SE)	-2.3 (0.4)	-3.0 (0.4)	-1.0 (0.4)
	Difference from placebo (97.5% CI)	-1.3 (-2.4, -0.1)	-2.0 (-3.1, -0.8)	
	p-value (two-sided)	.015	<.001	
CDER Reviewer's Analysis	N	153	153	154
	Baseline, Mean (SD)	96.8 (18.6)	97.6 (18.3)	98.2 (21.9)
	Change at Week 39 (SE)	-2.4 (0.4)	-3.0 (0.4)	-0.8 (0.4)
	Difference from placebo (97.5% CI)	-1.6 (-2.8, -0.4)	-2.2 (-3.4, -1.0)	
	p-value (two-sided)	.009	<.001	

Efficacy Result on Body Weight, CLP-105

Body Weight (kg) Change from Baseline at Week 52

		ITCA 650 20/60 mcg/day	sitagliptin 100 mcg/day
Applicant's Analysis	N	263	257
	Baseline, Mean (SD)	92.2 (19.9)	92.0 (21.4)
	Change at Week 52 (SE)	-4.0 (0.3)	-1.2 (0.4)
	Difference from sitagliptin (95% CI)	-2.7 (-3.7, -1.8)	
CDER Reviewer's Analysis	N	265	265
	Baseline, Mean (SD)	92.2 (19.9)	92.4 (21.3)
	Change at Week 52 (SE)	-2.9 (0.4)	-1.1 (0.4)
	Difference from sitagliptin (95% CI)	-1.8 (-2.8, -0.8)	

* For both the Applicant's and CDER's analyses, p-value (two-sided, superiority test) < .001.

Conclusion

- The CDER reviewer's analyses support the conclusion that ITCA 650 was efficacious when compared to either placebo or sitagliptin
  - Statistically significant results were found in both change from baseline (CFB) in A1C (the primary endpoint) and CFB in body weight (the key secondary endpoint) when compared to placebo (CLP-103) or sitagliptin (CLP-105)
  - The efficacy results from the reviewer's analyses were generally of smaller magnitude and had larger variability than those from the Applicant’s analyses
- However, due to issues such as high missing data rate and mismatched visit windows, how to determine a reliable estimate for the underlying treatment effect remains unclear

Clinical Safety Presentation and Summary of CDER's Overall Conclusions

Endocrinologic and Metabolic Drugs Advisory Committee Meeting
September 21, 2023

Michelle Carey, MD, MPH
Associate Director for Therapeutic Review
Division of Diabetes, Lipid Disorders, and Obesity (DDLO)
Office of New Drugs (OND)
CDER, FDA

Outline—Key Safety Issues/Summary

- Gastrointestinal Adverse events in FREEDOM
- Acute Kidney Injury (AKI) Safety Signal
  - AKI in ITCA 650 Phase 3 Program with focus on FREEDOM
  - AKI across GLP1RA CVOTs
- Major Adverse Cardiovascular Events (MACE)
  - MACE findings in FREEDOM
  - MACE data across GLP1RA CVOTs
  - All-cause mortality in FREEDOM and across GLP1RA CVOTs
- Serious adverse events (SAEs) in FREEDOM and across GLP1RA CVOTs
- Summary of CDER's Overall Conclusions

Approved GLP1RAs Are Commonly Associated with GI AEs

- Common adverse reactions of GLP1RAs relate to gastrointestinal (GI) tolerability:
  - Nausea, vomiting, diarrhea
- Dosing schedule for approved GLP1RAs, including exenatide-containing products:
  - Generally include a titration period of several weeks
  - Intended to gradually escalate exposures and thereby mitigate GI tolerability issues
- Conversely, rapid increases in exposure can cause GI adverse reactions

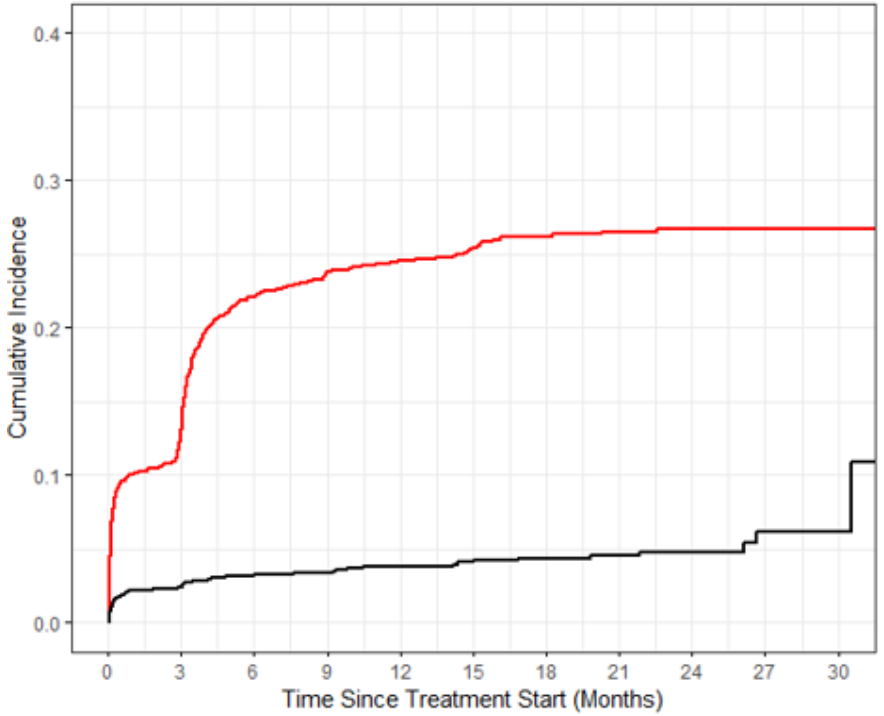
Adverse Events of Nausea, Vomiting, and Diarrhea* in FREEDOM (On-Treatment)

	ITCA 60 mcg/day (n=2070) N (Events per 100 PY)	Placebo (n=2074) N (Events per 100 PY)	Rate Difference (Events per 100 PY)	Rate Ratio
Nausea (All)	564 (25)	86 (3)	22	7.8
Mild	330 (14)	59 (2.2)	13.4	6.4
Moderate	197 (7.9)	24 (0.9)	8.1	8.9
Severe	37 (1.4)	3(0.1)	1.8	12.9
All vomiting	392 (16)	26 (1)	15.2	16.9
Mild	238 (9.5)	17 (0.6)	10.2	15.2
Moderate	125 (4.9)	7 (0.3)	5.5	19.1
Severe	29 (1.1)	2 (0.1)	1.4	15.1
All diarrhea	198 (8)	87 (3)	4.7	2.4
Mild	128 (5.1)	56 (2.1)	4	2.4
Moderate	65 (2.5)	30 (1.1)	2.1	2.3
Severe	5 (0.2)	1 (0)	0.3	5.2

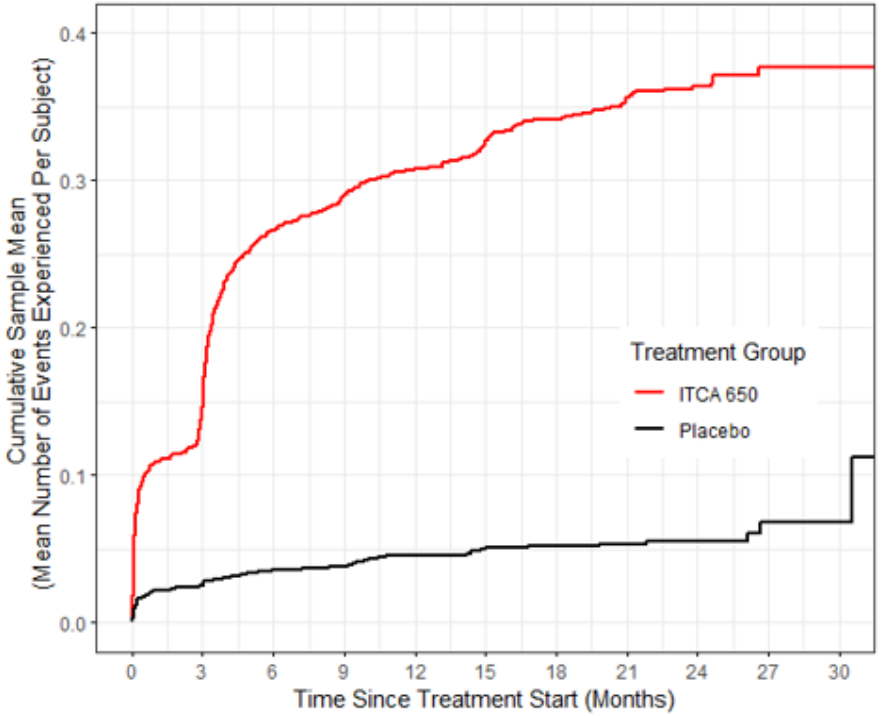
Source: CDER Review staff
Investigator attribution of intensity
*Events were identified using Narrow FDA Medical Queries (ver. 2.1)

Cumulative Incidence and Cumulative Sample Mean for Nausea and Vomiting (On-Treatment Narrow FMQ)

Time to First Event



All Events



Source: CDER Review staff

Acute Kidney Injury Safety Signal in ITCA 650 Clinical Program

- AKI was evaluated as an adverse event of special interest based on standard spontaneous adverse event (AE) reporting
  - Specific prospective ascertainment methods were not employed (e.g., dedicated Case Report Forms)
  - Narratives provided only for those events coded as serious AEs
  - The Applicant specified that they queried the safety database using the Acute Renal Failure Standardized MedDRA Query (SMQ, version 18.1, Narrow scope)*
- 46 subjects (1.8%) with 52 AKI events in the ITCA 20/60 mcg/day treatment arms
- 25 subjects (1.0%) with 27 AKI events in comparator arms

*__Preferred Terms__: Acute kidney injury, Acute phosphate nephropathy, Acute prerenal failure, Azotaemia, Continuous haemodiafiltration, Dialysis, Haemodialysis, Haemofiltration, Neonatal anuria, Nephropathy toxic, Oliguria, Peritoneal dialysis, Prerenal failure, Renal failure, Renal failure neonatal, Renal impairment, Renal impairment neonatal

Acute Kidney Injury Safety Signal: Serious AKI Events

- AKI serious adverse events (SAEs) occurred in 14 subjects (0.6%) who received ITCA 650 vs 4 subjects (0.2%) who received placebo
  - All but one AKI SAE occurred in FREEDOM
  - 11 of 14 AKI SAEs in the ITCA 650 treatment arms were preceded by gastrointestinal symptoms with clinical narratives consistent with dehydration precipitating the event
  - Seven (7) AKI SAEs occurred in subjects with the initiation device: ITCA 650 20 mcg/day implant
- Review of death narratives identified two subjects with AKI events coded as non-serious in subjects who died

Serious and Nonserious AKI Imbalance in FREEDOM Unfavorable to ITCA 650

		Ascertainment Window	ITCA 650 (N=2070) n (%) [Events] IR	Placebo (N=2074) n (%) [Events] IR	HR (95% CI)	IR Difference Incidence/100 PY (95% CI)
FMQ	Broad	OS	66 (3.19) [84] 2.29	40 (1.93) [50] 1.38	1.67 (1.12-2.47)	0.91 (0.22-1.61)
		OT	62 (3) [78] 2.39	39 (1.88) [49] 1.44	1.65 (1.11-2.46)	0.95 (0.20-1.70)
	Narrow	OS	20 (0.97) [21] 0.68	5 (0.24) [5] 0.17	4.04 (1.52-10.76)	0.51 (0.18-0.85)
		OT	18 (0.87) [19] 0.69	5 (0.24) [5] 0.18	3.72 (1.38-10.02)	0.50 (0.15-0.86)
SMQ	Broad	OS	75 (3.62) [96] 2.61	47 (2.27) [58] 1.62	1.61 (1.12-2.32)	0.99 (0.24-1.74)
		OT	71 (3.43) [90] 2.75	46 (2.22) [57] 1.71	1.61 (1.11-2.33)	1.04 (0.24-1.85)
	Narrow	OS	42 (2.03) [48] 1.45	24 (1.16) [26] 0.82	1.76 (1.07-2.91)	0.63 (0.08-1.17)
		OT	39 (1.88) [44] 1.5	24 (1.16) [26] 0.88	1.68 (1.01-2.79)	0.61 (0.02-1.2)

Abbreviations: FMQ - FDA MedDRA Query; SMQ – Standardized MedDRA Query; IR – Incidence Rate; OT – On Treatment; OS – On Study;

Source: CDER Review staff

Serious AKI Imbalance in FREEDOM Unfavorable to ITCA 650

		Ascertainment Window	ITCA 650 (n=2070) N (%) [Events] IR	Placebo (n=2074) N (%) [Events] IR	HR (95% CI)	IR Difference Incidence/100 PY (95% CI)
FMQ	Broad	OS	14 (0.68) [14] 0.48	4 (0.19) [4] 0.14	3.52 (1.16-10.70)	0.34 (0.06-0.63)
		OT	13 (0.63) [13] 0.5	4 (0.19) [4] 0.15	3.33 (1.09-10.21)	0.35 (0.04-0.65)
	Narrow	OS	10 (0.48) [10] 0.34	3 (0.14) [3] 0.1	3.35 (0.92-12.18)	0.24 (0-0.48)
		OT	9 (0.43) [9] 0.34	3 (0.14) [3] 0.11	3.09 (0.84-11.4)	0.23 (-0.02-0.49)
SMQ	Broad	OS	14 (0.68) [14] 0.48	4 (0.19) [4] 0.14	3.52 (1.16-10.7)	0.34 (0.06-0.63)
		OT	13 (0.63) [13] 0.5	4 (0.19) [4] 0.15	3.33 (1.09-10.21)	0.35 (0.04-0.65)
	Narrow	OS	13 (0.63) [13] 0.44	4 (0.19) [4] 0.14	3.27 (1.07-10.03)	0.31 (0.03-0.59)
		OT	12 (0.58) [12] 0.46	4 (0.19) [4] 0.15	3.08 (0.99-9.54)	0.31 (0.02-0.61)

Abbreviations: FMQ - FDA MedDRA Query; SMQ – Standardized MedDRA Query; IR – Incidence Rate; OT – On Treatment; OS – On Study;

Source: CDER Review staff

Serious AKI Events - Key Clinical Features

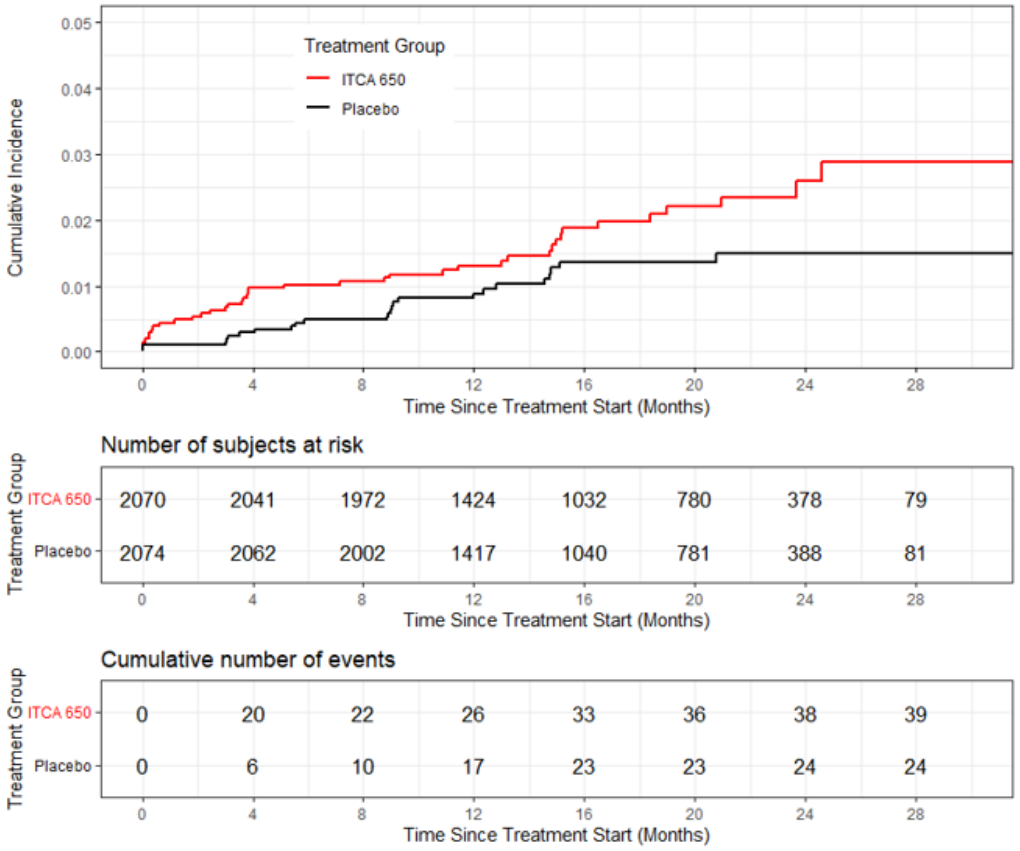
- Baseline risk factors for AKI were balanced between treatment arms due to randomization
  - concomitant medications
  - baseline renal impairment
- 11 of 14 serious AKI events in the ITCA 650 treatment arm were preceded by GI symptoms
- Timing of events in ITCA 650 treatment arm:
  - 0 to 109 days after device placement or replacement
- 2 subjects in the ITCA 650 treatment arm required dialysis (1 coded as serious, the other a subject who died in the setting of an AKI event coded as non-serious); 1 subject in the placebo required dialysis

AKI Imbalance in FREEDOM Number Needed to Harm

- For the more clinically relevant events of serious AKI:
  - a number needed to harm (NNH) of **322 patients*** treated with ITCA 650 per year to result in one additional serious AKI event

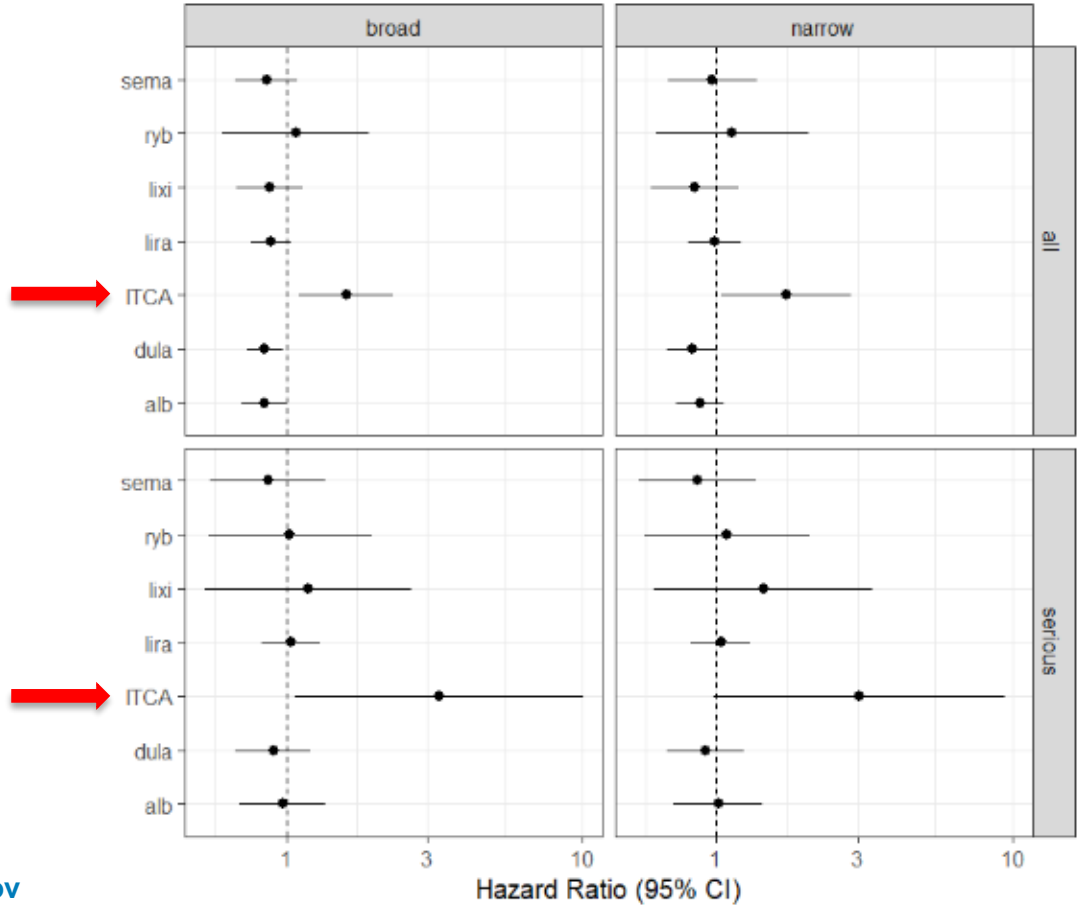
*95% CI 164-5000 (OT censoring) vs. 95% CI 169-3333 (OS censoring)

Kaplan-Meier Plot for Serious and Nonserious AKI in CLP-107 (FREEDOM) (SMQ Acute Renal Failure – Narrow)* OT



Source: CDER Review staff

Hazard Ratios for Time to First Occurrence of AKI (ARF SMQ-narrow) for Marketed GLP1RA CVOTs*



Legend: sema=semaglutide (SUSTAIN-6), ryb=oral semaglutide (PIONEER-6), lixi=lixisenatide (ELIXA), ITCA=exenatide (FREEDOM), dula=dulaglutide (REWIND), alb=albiglutide (HARMONY)

*EXSCEL (Bydureon CVOT) was a large streamlined postmarket study that did not collect AKI data with MedDRA coding, so is not included in this analysis

Source: CDER Review staff

Baseline Characteristics Across GLP1RA CVOTs

	Trials in Subjects with or at risk of CVD								Trial in Subjects post-ACS
	EXSCEL[1] Exenatide N=14,752	AMPLITUDE-0[2] Efpeglenatide N=4076	LEADER[3] Liraglutide N=9340	SUSTAIN-6[4] Semaglutide N=3297	PIONEER-6[5] Semaglutide N=3183	REWIND[6] Dulaglutide N=9901	HARMONY[7] Albiglutide N=9463	FREEDOM[8] Exenatide N=4156	ELIXA[9,10] Lixisenatide N=6068
Median duration (years)	3.2	1.8	3.8	2.1	1.3	5.4	1.6	1.4	2.1
Established CVD (%)	73	90	81	83	85	32	100	76	100
Age (years)	62	65	64	65	66	66	64	62	60
A1C (%)	8.1	8.9	8.7	8.7	8.2	7.3	8.7	8.3	7.7
Diabetes duration (years)	13	15	13	14	15	10	14	11	9
BMI (kg/m^2)	32	33	33	33	32	32	32	33	30
eGFR ≥90 mL/min/1.73m^2 (%)	29	NR	35	30	29	27	30	30	23
eGFR 60-89 mL/min/1.73m^2 (%)	49	NR	42	42	44	51	47	60	53
eGFR <60 mL/min/1.73m^2 (%)	22	31	23	29	27	23	23	10	23

[1]Holman et al. (2017), [2]Gerstein et al. (2021),[3]Marso et al. (2016a),[4]Marso et al. (2016b), [5]Husain et al. (2019),[6]Gerstein et al. (2019),[7]Hernandez et al. (2018),[8]Ruff et al. (2022),[9]Pfeffer et al. (2015)

Abbreviations: ACS, acute coronary syndrome; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; CVOT, cardiovascular outcomes trial; eGFR, estimated glomerular filtration rate; GLP1RA, glucagon-like peptide-1 receptor agonist; A1C, hemoglobin A1C; HR, hazard ratio; MACE, major adverse cardiovascular event; NR, not reported

AKI in LEADER

Table 19 Summary of selected safety areas in LEADER

	Liraglutide				Placebo			
	N	(%)	E	R	N	(%)	E	R
Number of patients	4668				4672			
Patient-years of observation	17822				17741			
Event types identified by MedDRA search[a]								
Acute renal failure	156	(3.3)	179	1.00	152	(3.3)	171	0.96
Serious	141	(3.0)	164	0.92	136	(2.9)	153	0.86
Severe	82	(1.8)	88	0.49	77	(1.6)	82	0.46
Fatal	16	(0.3)	16	0.09	13	(0.3)	14	0.08
Leading to permanent discontinuation of trial product	19	(0.4)	19	0.11	23	(0.5)	23	0.13

Source: Novo Nordisk Briefing Document to EMDAC June 20, 2017, p. 75

Nephropathy Endpoint in LEADER

	Liraglutide N=4668	Placebo N=4672
Proportion of patients with nephropathy at end of trial	5.7%	7.2%
New onset of persistent macroalbuminuria	3.4%	4.6%
Persistent doubling of serum creatinine*	1.9%	2.1%
Need for continuous renal replacement therapy	1.2%	1.4%
Death due to renal disease	0.2%	0.1%

*Persistent doubling of serum creatinine and eGFR <=45 ml/min/1.73 m2 per MDRD

- "Non-cardiovascular 'renal' deaths by post-hoc classification: liraglutide 11 (0.2%) vs. placebo 5 (0.1%)
  - –Review of narratives indicated most were related to worsening of chronic renal failure"
- "No clear cases of liraglutide-induced gastrointestinal losses leading to acute renal failure deaths"

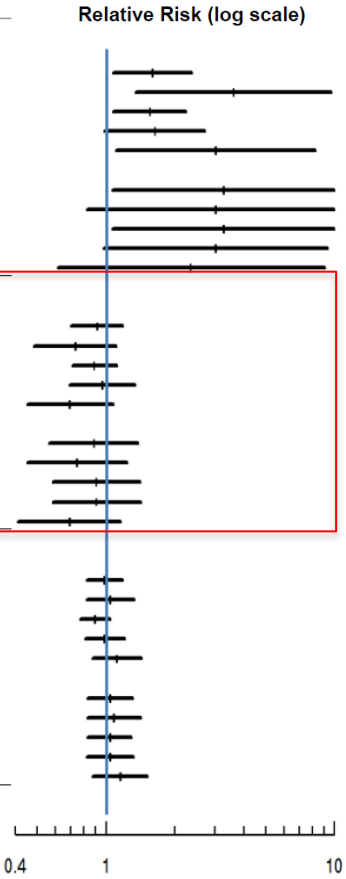
Source: FDA presentation to EMDAC June 20, 2017, slide 44 (Clinical Efficacy Overview)

AKI SAEs in SUSTAIN-6: No Imbalance Reported at Clinicaltrials.gov

Renal and Urinary Disorders	Semaglutide 0.5 mg		Semaglutide 1.0 mg		Placebo 0.5 mg		Placebo 1.0 mg	
N		826		822		824		825
	n (%)	Events	n (%)	Events	n (%)	Events	n (%)	Events
Acute kidney injury	18 (2.2)	22	6 (0.7)	8	14 (1.7)	14	22 (2.7)	24
Acute prerenal failure	1 (0.1)	1	0 (0)	0	0 (0)	0	0 (0)	0
Azotaemia	1 (0.1)	1	0 (0)	0	0 (0)	0	0 (0)	0
Renal failure	2 (0.2)	2	3 (0.4)	3	1 (0.1)	1	1 (0.1)	1
Renal impairment	3 (0.4)	3	1 (0.1)	1	3 (0.4)	3	1 (0.1)	1
Anuria	1 (0.1)	1	0 (0)	0	0 (0)	0	0 (0)	0
Total	26 (3.1)	30	10 (1.2)	12	18 (2.2)	18	24 (2.9)	26
Total Pooled (0.5 mg and 1.0 mg arms)			36 (2.2)	42			42 (2.5)	44

Analyses of AKI in FREEDOM, SUSTAIN-6 and LEADER

	Drug N	Placebo N	RR	95% CI
FREEDOM	2075	2081		
Serious + non-serious				
Acute Kidney Injury FDA B	62	39	**1.59**	(1.07, 2.37)
Acute Kidney Injury FDA N	18	5	**3.61**	(1.34, 9.71)
Acute Renal Failure SMQ B	71	46	**1.55**	(1.07, 2.23)
Acute Renal Failure SMQ N	39	24	**1.63**	(0.98, 2.7)
AKI	15	5	**3.01**	(1.1, 8.26)
Serious				
Acute Kidney Injury FDA B	13	4	**3.26**	(1.06, 9.98)
Acute Kidney Injury FDA N	9	3	**3.01**	(0.82, 11.1)
Acute Renal Failure SMQ B	13	4	**3.26**	(1.06, 9.98)
Acute Renal Failure SMQ N	12	4	**3.01**	(0.97, 9.31)
AKI	7	3	**2.34**	(0.61, 9.04)
SUSTAIN-6	1648	1649		
Serious + non-serious				
Acute Kidney Injury FDA B	100	110	**0.91**	(0.7, 1.18)
Acute Kidney Injury FDA N	37	51	**0.73**	(0.48, 1.1)
Acute Renal Failure SMQ B	130	147	**0.88**	(0.71, 1.11)
Acute Renal Failure SMQ N	65	68	**0.96**	(0.69, 1.33)
AKI	34	49	**0.69**	(0.45, 1.07)
Serious				
Acute Kidney Injury FDA B	36	41	**0.88**	(0.56, 1.37)
Acute Kidney Injury FDA N	26	35	**0.74**	(0.45, 1.23)
Acute Renal Failure SMQ B	37	41	**0.90**	(0.58, 1.4)
Acute Renal Failure SMQ N	36	40	**0.90**	(0.58, 1.41)
AKI	24	35	**0.69**	(0.41, 1.15)
LEADER	4668	4672		
Serious + non-serious				
Acute Kidney Injury FDA B	228	232	**0.98**	(0.82, 1.18)
Acute Kidney Injury FDA N	133	128	**1.04**	(0.82, 1.32)
Acute Renal Failure SMQ B	299	336	**0.89**	(0.77, 1.04)
Acute Renal Failure SMQ N	186	189	**0.98**	(0.81, 1.2)
AKI	127	114	**1.11**	(0.87, 1.43)
Serious				
Acute Kidney Injury FDA B	149	144	**1.04**	(0.83, 1.3)
Acute Kidney Injury FDA N	111	103	**1.08**	(0.83, 1.41)
Acute Renal Failure SMQ B	151	146	**1.04**	(0.83, 1.29)
Acute Renal Failure SMQ N	141	136	**1.04**	(0.82, 1.31)
AKI	108	94	**1.15**	(0.87, 1.51)



Source: CDER Analysis, July 30, 2020

GLP1RA Class Labeling for AKI

- Class labeling for GLP1RA products includes a **Warning and Precaution** for AKI
- Class labeling is based on postmarketing reports of AKI for Byetta and Victoza sent to the FDA Adverse Events Reporting System (FAERS)
  - FAERS is a voluntary adverse event reporting system and is subject to a variety of limitations
  - FAERS cannot be used to determine the magnitude, incidence, or prevalence of AKI with GLP1RA products
- No approved GLP1RA product had an AKI imbalance in their premarket or postmarket clinical trials, suggesting that the AKI risk may be greater with ITCA 650 versus approved products

Summary of CDER Conclusions on AKI

- Imbalance in overall and serious AKI events in subjects who received ITCA 650 versus comparators
  - The imbalance was apparent despite lower susceptibility of the FREEDOM population vs. other CVOTs given the lower number of CKD subjects enrolled in FREEDOM
- Serious AKI events
  - The data suggest an approximately 3 to 3.5-fold increased risk (NNH 322 in a controlled setting, in a population with low background frequency of CKD)
  - Most serious AKI events were preceded by GI symptoms
- Device and PK exposure data demonstrating the potential for abrupt increases in exenatide exposures
  - Could reasonably cause GI AEs leading to dehydration and AKI
  - AKI signal could plausibly be related to treatment with ITCA 650
- This safety issue should be addressed via submission of additional premarket clinical data

Major Adverse Cardiovascular Events (MACE)

Guidance for Industry

Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

December 2008
Clinical/Medical

FDA

- Premarket safety data should show that the upper bound of the two-sided 95% confidence interval for the estimated risk ratio for important cardiovascular events is less than 1.8 (i.e., excludes an 80% increase)
- "…it would not be reassuring to find a point estimate of 1.5 (a nominally significant increase) even if the 95 percent upper bound was less than 1.8."
- If the "upper bound of the two-sided 95% confidence interval for the estimated increased risk (i.e., risk ratio) is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3."
- Resulted in widespread conduct of CVOTs to evaluate new antihyperglycemic agents, including all of the GLP1RA CVOTs

ITCA 650 CV Risk Assessment

- Primary composite CV endpoint: **4-point MACE** (CV death, MI, non-fatal stroke, unstable angina (UA))
- Secondary composite CV endpoint: **3-point MACE** (CV death, MI, non-fatal stroke)

- Analyses of composite endpoints using Cox proportional hazard models were conducted for pooled MACE data (CLP-103, CLP-105, CLP-107) and CLP-107 (FREEDOM) individually:
  - Time to first occurrence of any event in the 4-point MACE composite endpoint
  - Time to first occurrence of any event in the 3-point MACE composite endpoint
- The following censoring schemes were applied:
  - Analysis of all positively adjudicated events that occurred at any time during study participation ("end of study (EOS)" or "On-Study censoring")
  - Analysis of all positively adjudicated events that occurred up to 30 days after discontinuation of ITCA 650/placebo ("end of treatment (EOT) + 30 days" or "On-Treatment + 30 days censoring")
  - Analysis of all positively adjudicated events that occurred prior to discontinuation of ITCA 650/placebo ("end of treatment (EOT)" or "On-Treatment censoring")

MACE Pooling Strategy

- FREEDOM was designed to continue until 124 positively adjudicated events were collected across FREEDOM, Study CLP-103, and Study CLP-105
- For the planned pooled analyses in the ITCA 650 program, similar event ascertainment strategies were used (e.g., adjudication)
- Challenges of interpreting pooled analyses include:
  - Differences in the enrolled trial populations with T2DM
    - CLP-103 and CLP-105 enrolled younger, healthier subjects at low CV risk
    - CLP-107 enrolled older subjects at high CV risk
  - Differential follow-up due to study designs
    - CLP-103 and CLP-105 utilized a fixed study endpoint (i.e., A1C at 6 months)
    - FREEDOM was an event-driven trial

Time to First Occurrence of 3-point MACE and 4-point MACE - ITT Population **End of Study**, Pooled Analyses of CLP-103, CLP-105, FREEDOM; and FREEDOM only

	ITCA 650 Number of events/Total No. (%) IR (n/100 PY)	Control Number of events/Total No. (%) IR (n/100 PY)	HR (95% CI)**
3-Point MACE* Pooled	85/2649 (3.2%) 2.47	75/2502 (3.0%) 2.25	1.13 (0.82,1.54)
4-Point MACE Pooled	96/2649 (3.6%) 2.80	85/2502 (3.4%) 2.56	**1.12 (0.84, 1.50)**
3-Point MACE FREEDOM	85/2075 (4.1%) 2.94	69/2081 (3.3%) 2.37	1.24 (0.90, 1.70)
4-Point MACE FREEDOM	95/2075 (4.6%) 3.29	79/2081 (3.8%) 2.72	1.21 (0. 90, 1.63)

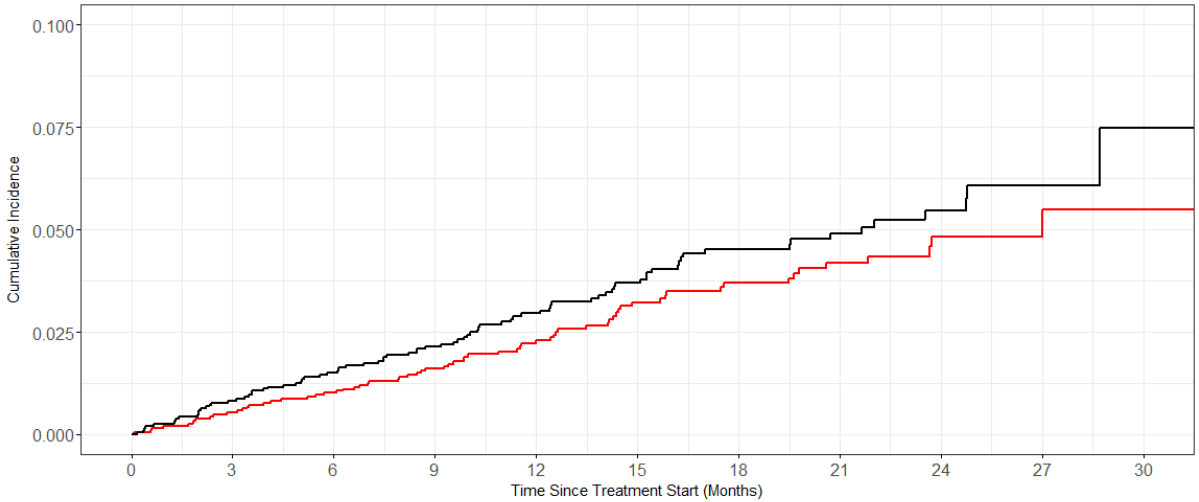
 *160 positively adjudicated 3-point MACE events (154 in FREEDOM, 6 in glycemic control trials) Source: CDER Review staff

Time to First Occurrence of 3-Point MACE and 4-Point MACE– ITT Population **End of Treatment,** Pooled Analyses of CLP-103, CLP-105, and FREEDOM; and FREEDOM only

	ITCA 650 Number of events/Total No. (%) IR (n/100 PY)	Control Number of events/Total No. (%) IR (n/100 PY)	HR (95% CI)**
3-Point MACE Pooled	73/2641 (2.8%) 2.54	61/2493 (2.4%) 2.11	1.24 (0.88, 1.74)
4-Point MACE Pooled	83/2641 (3.1%) 2.9	71/2493 (2.8%) 2.5	1.20 (0.87, 1.66)
3-Point MACE FREEDOM	73/2070 (3.0%) 2.97	56/2074 (2.9%) 2.26	1.36 (0.96, 1.92)
4-Point MACE FREEDOM	82/2070 (4.0%) 3.4	66/2074 (3.2%) 2.6	1.29 (0.93, 1.79)

Source: CDER Review staff

Kaplan-Meier Plot for Time to First Occurrence of 3-Point MACE – ITT Population End of Study, FREEDOM



Number of subjects at risk

Placebo	2081	2068	2047	1828	1414	1146	919	691	390	142	37
ITCA 650	2075	2053	2028	1805	1415	1150	914	672	377	146	33

Cumulative number of events

Placebo	0	11	21	33	44	56	61	65	68	68	69
ITCA 650	0	17	31	44	57	67	76	79	82	84	85

Source: CDER Review staff

Key Subgroup Analyses:
Pooled Analyses and FREEDOM, On-Study

Subgroup	3-point MACE (Pooled)	4-point MACE (Pooled)	3-point MACE (FREEDOM)	4-point MACE (FREEDOM)
Age ≥65 years				
Drug, n (%)	41 (4.4)	43 (4.7)	41 (5.0)	43 (5.2)
Comparator, n (%)	23 (2.6)	26 (3.0)	22 (2.7)	25 (3.1)
HR (95% CI)	1.79 (1.08, 2.99)	1.67 (1.02, 2.71)	1.88 (1.12, 3.15)	1.73 (1.06, 2.84)
eGFR <60 mL/min/1.73m²				
Drug, n (%)	13 (6.2)	13 (6.2)	13 (6.6)	13 (6.6)
Comparator, n (%)	6 (2.6)	7 (3.1)	6 (2.8)	7 (3.3)
HR (95% CI)	2.32 (0.88, 6.12)	2.0 (0.80, 5.01)	2.32 (0.88, 6.12)	2.00 (0.80, 5.01)

Source: CDER Review staff; software: R v. 4.2; script: MACE_analysis. R; data: adef.xpt, adsl.xpt (SDN0000); subgroup HR estimated using primary analysis model on subsetted data (Cox proportional hazards model with treatment [ITCA 650 or control], study and CV risk as strata). On-study analysis.
Abbreviations: CV, cardiovascular; eGFR, estimated glomerular filtration rate; HR, hazard ratio; IR, incidence rate; ITCA 650, exenatide in DUROS device; MACE, major adverse cardiovascular event

Time to CV Death, Nonfatal MI, and Nonfatal Stroke with Three Methods of Censoring - CV Death and Nonfatal MI Drove the MACE Imbalance

		ITCA 650 n/N (%) [IR] (n/100 PY)	Control n/N (%) [IR] (n/100 PY)	HR (95% CI)
CV Death	On Study	28/2075 (1.3) [0.95]	23/2081 (1.1) [0.78]	1.22 (0.70, 2.12)
	On Treatment +30	26/2070 (1.3) [0.99]	20/2074 (1.0) [0.73]	1.35 (0.75, 2.42)
	On Treatment	26/2070 (1.3) [1.05]	18/2074 (0.9) [0.70]	1.50 (0.82, 2.73)
Nonfatal MI	On Study	37/2075 (1.8) [1.27]	28/2081 (1.3) [0.96]	1.33 (0.82, 2.18)
	On Treatment +30	33/2070 (1.6) [1.27]	24/2070 (1.1) [0.88]	1.43 (0.84, 2.41)
	On Treatment	31/2070 (1.5) [1.26]	22/2070 (1.1) [0.86]	1.47 (0.85, 2.43)
Nonfatal Stroke	On Study	23/2075 (1.1) [0.79]	23/2081 (1.1) [0.78]	1.00 (0.56, 1.79)
	On Treatment +30	21/2070 (1.0) [0.80]	19/2074 (0.9) [0.74]	1.03 (0.55, 1.95)
	On Treatment	19/2070 (0.9) [0.77]	19/2074 (0.9) [0.74]	1.03 (0.56, 1.89)

n: Number of Subjects with Event; N – Number of Subjects; % - Percent of Subjects with Event;
IR – Incidence Rate (Incidence per 100 Patient-Years of Observation)

Source: CDER Review staff

Comparison of 3-Point and 4-Point MACE and All-Cause Mortality Across CVOTs in the GLP1RA Class

CVOT	EXSCEL[1]	AMPLITUDE-0[2]	LEADER[3]	SUSTAIN-6[4]	PIONEER-6[5]	REWIND[6]	HARMONY[7]	FREEDOM[8]	ELIXA[9,10]
GLP1RA	Exenatide	Efpeglenatide	Liraglutide	Semaglutide	Semaglutide	Dulaglutide	Albiglutide	Exenatide	Lixisenatide
3-Point MACE									
Drug, n (%)	839 (11.4)	189 (7.0)[12]	608 (13.0)	108 (6.6)	61 (3.8)	594 (12.0)	338 (7.1)	**85 (4.1)**	400 (13.2)
Placebo, n (%)	905 (12.2)	125 (9.2)	694 (14.9)	146 (8.9)	76 (4.8)	663 (13.4)	428 (9.0)	**69 (3.3)**	392 (12.9)
HR (95% CI)	0.91 (0.83, 1.0)	0.73 (0.58,0.93)	0.87 (0.78, 0.97)	0.74 (0.58, 0.95)	0.79 (0.57, 1.11)	0.88 (0.79, 0.99)	0.78 (0.68, 0.90)	**1.24 (0.90, 1.70)**	1.02 (0.89, 1.17)
4-Point MACE[11]									
Drug, n (%)	NR[11]	NR	NR	NR	NR	666 (13.5)	373 (7.9)	**95 (4.6)**	406 (13.4)
Placebo, n (%)	NR[11]	NR	NR	NR	NR	720 (14.5)	468 (9.9)	**79 (3.8)**	399 (13.2)
HR (95% CI)	NR[11]	NR	NR	NR	NR	0.91 (0.82,1.01)	0.78 (0.69, 0.90)	**1.21 (0.90, 1.63)**	1.02 (0.89, 1.17)
All-cause mortality									
Drug, n(%)	507 (6.9)	111 (4.1)	381 (8.4)	62 (3.8)	23 (1.4)	536 (10.8)	196 (4.1)	**49 (2.4)**	211 (7.0)
Placebo, n(%)	584 (7.9)	69 (5.1)	461 (9.9)	61 (3.7)	45 (2.8)	592 (12.0)	205 (4.3)	**41 (2.0)**	223 (7.4)
HR (95% CI)	0.86 (0.77,0.97)	0.78 (0.58,1.06)	0.85 (0.74, 0.97)	1.05 (0.74, 1.50)	0.51 (0.31, 0.84)	0.90 (0.80, 1.01)	0.95 (0.79, 1.16)	**1.20 (0.79, 1.81)**	0.94 (0.78, 1.13)

[1]Holman et al. (2017), [2]Gerstein et al. (2021),[3]Marso et al. (2016a),[4]Marso et al. (2016b), [5]Husain et al. (2019),[6]Gerstein et al. (2019),[7]Hernandez et al. (2018),[8]Ruff et al. (2022),[9]Pfeffer et al. (2015)

[10] The study population in ELIXA differed from those in the other studies included in this table. ELIXA enrolled a post-acute coronary syndrome (post-ACS) population.

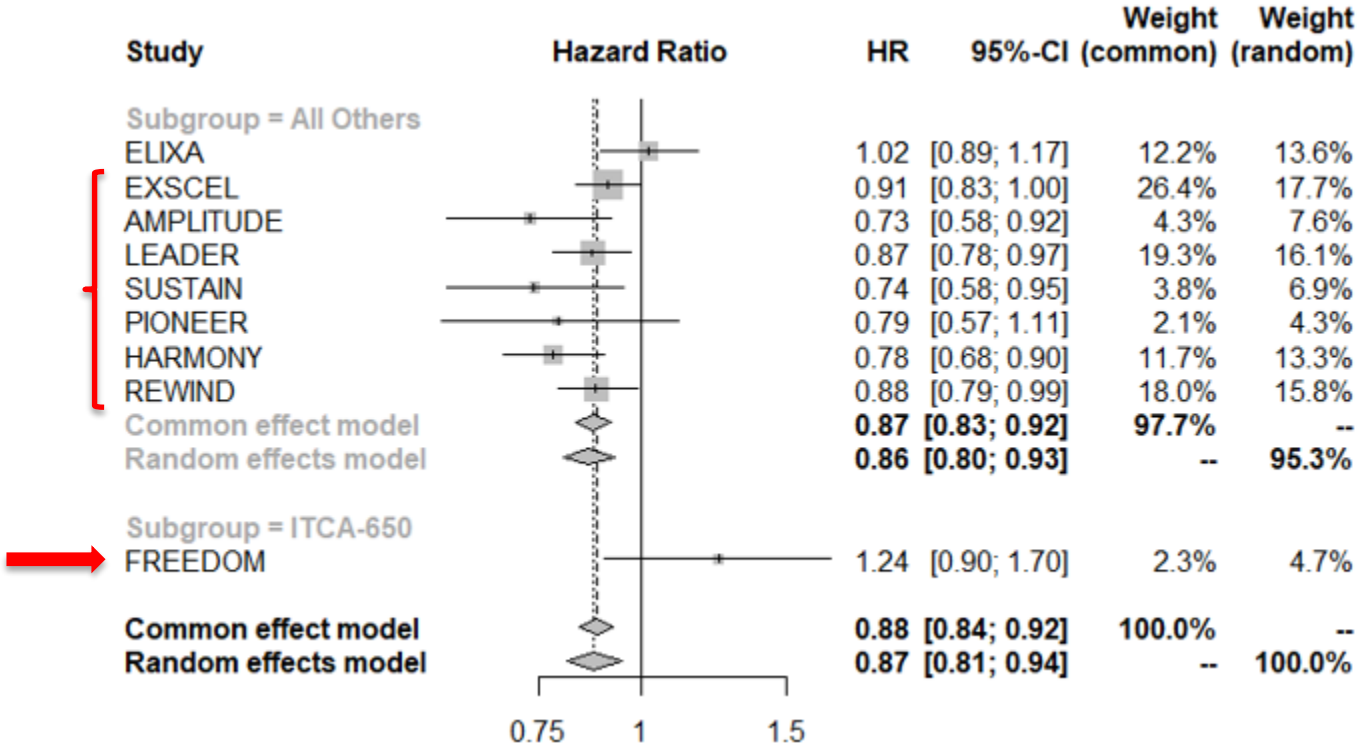
[11] Four-point MACE (CV death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina) was the primary efficacy endpoint in ELIXA and FREEDOM. For all other CVOTs in the GLP1RA class the primary efficacy endpoint was 3-point MACE (CV death, nonfatal MI, nonfatal stroke).

[12] AMPLITUDE utilized a 2:1 randomization scheme.

ELIXA Precedent: Lixisenatide Was Approved After CDER's Review of Final ELIXA Results

- NDA for lixisenatide submitted December 2012
  - ELIXA interim analysis for the primary composite 4-point MACE: **HR 1.14 (95% CI 0.89, 1.47)**
- Applicant withdrew the NDA September 2013
  - The Applicant decided that CDER's evaluation of lixisenatide should be based on the complete results of the ELIXA study rather than interim data
- NDA for lixisenatide resubmitted and approved in 2016 with final ELIXA results available:
  - 4-point MACE **HR 1.02 (95% CI 0.89, 1.17)**

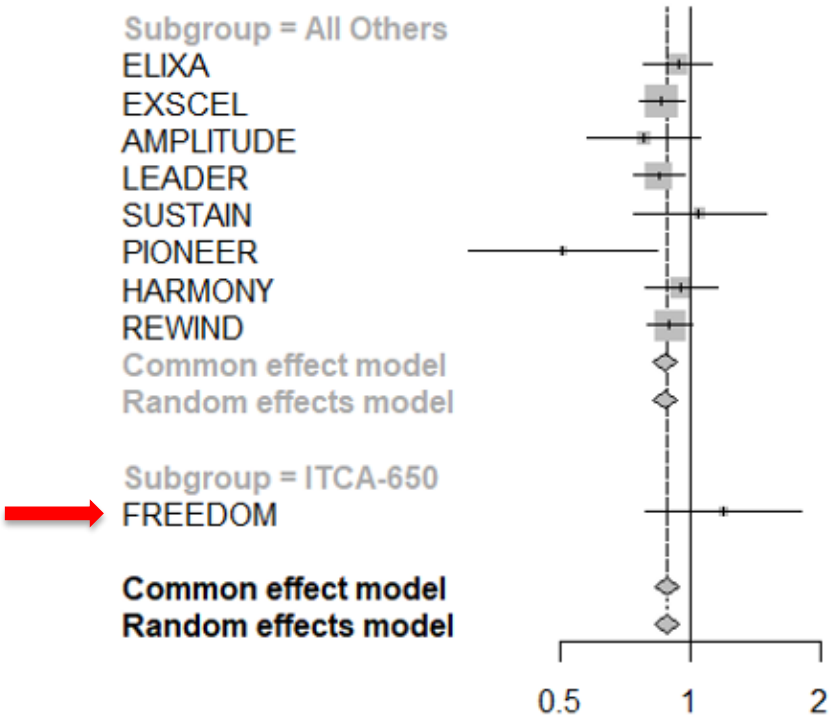
Meta-Analysis of 3-Point MACE Across CVOTs in the GLP1RA Class



CI: confidence interval; EOS: end of study; HR: hazard ratio; ITCA 650: exenatide in DUROS device; MACE: major adverse cardiovascular event

Source: CDER Review staff

Meta-Analysis of All-Cause Mortality Across CVOTs in the GLP1RA Class



Source: CDER Review staff

Summary of CDER Conclusions on MACE

- Primary and secondary endpoint analyses and all other prespecified analyses of CV risk, regardless of pooling or censoring strategy utilized, provide consistent findings:
  - Results of FREEDOM, a dedicated CVOT which enrolled patients with T2DM at high CV risk, do not adequately exclude the possibility that ITCA 650 is associated with excess risk of CV harm
  - Although most of the analyses exclude an 80% increase in the risk of CV harm, not all do, and the point estimates of the observed hazard ratios are not reassuring

- FREEDOM is an outlier among the many other long-acting GLP1RA CVOTs:
  - the lower bound of the 95% CI for MACE (0.90) was higher than the point estimate of the HR observed HR in most individual GLP1RA CVOTs and in the meta-analysis (0.88)
  - raises concern that ITCA 650's CV safety profile is distinct from that of other GLP1RAs
  - fails to provide reassurance that ITCA 650 is not associated with an increase in CV risk

- The MACE data from FREEDOM constitute a CV signal that requires additional premarket investigation to ensure patients treated with the product are not exposed to excess CV risk

SAEs in FREEDOM

Time Point	ITCA 650 (N=2070) n (%) IR (n/100 PY)	Control (N=2074) n (%) IR (n/100 PY)	HR (95% CI)
End of treatment + 30 days	335 (16.2) 14.1	298 (14.4) 11.8	1.19 (1.02-1.39)
End of study	369 (17.8) 14.2	324 (15.6) 12.1	1.17 (1.01-1.36)

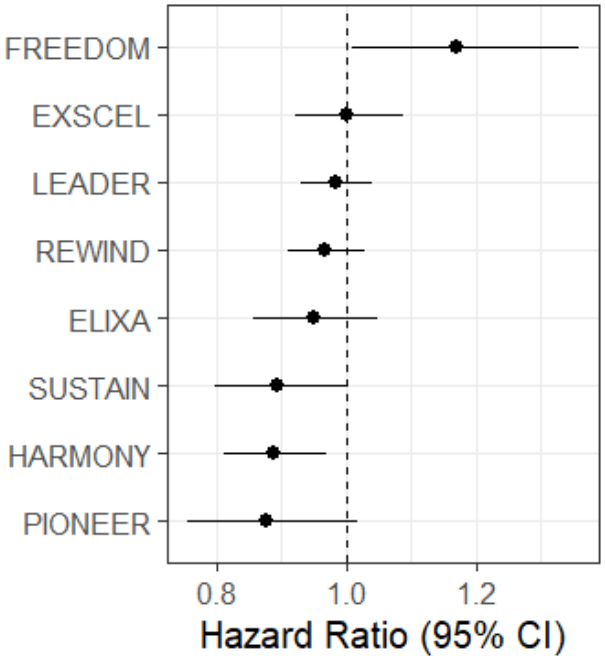
Source: CDER Review staff

SAE Imbalance in FREEDOM: Number Needed to Harm

An estimated number needed to harm (NNH) of **45*** treated with ITCA 650 per year to result in one additional serious adverse event

*95% CI: 23 - 442 (On-Treatment + 30 Days)
25 – 680 (On-Study)

Time to First Occurrence of SAE (Fatal and Nonfatal) in GLP1RA CVOTs, On-Study



Source: CDER Review staff

Summary of CDER Review Conclusions (1)

- Device data demonstrate inconsistent exenatide release even under ideal in vitro conditions
- PK data support the device review conclusions that exenatide release demonstrates high within-subject variability with the potential for rapid excursions
- ITCA 650 has demonstrated efficacy based on its glycemic lowering effect
- Clinical safety data are concerning, especially considering the therapeutic context of available GLP1RA therapies
  - AKI signal is concerning and plausibly related to treatment with ITCA 650 based on the available device and clinical pharmacology data
  - MACE results are dissimilar to findings from other large CVOTs in the class
  - Overall SAEs and all cause mortality trend unfavorably, also distinct from the class

Summary of CDER Review Conclusions (2)

- Benefit-Risk Assessment:
  - Benefit:
    - Glycemic efficacy
    - Potential for advantages inherent to the product presentation
      - Long-term adherence sufficient to improve outcomes compared to other approved products in the class has not been demonstrated
  - Risks:
    - AKI safety signal in the setting of inconsistent device release, PK variability, and GI AEs
    - Non-reassuring CV risk assessment
    - Unfavorable trends in SAEs and all-cause mortality
  - Overall: Significant uncertainties regarding the safety of ITCA 650 should be addressed through submission of additional premarket data

Back-up Slide

Risk Mitigation Strategies Considered

- **<u>Labeling strategies or REMS to address AKI risk were deemed inadequate:</u>**
  - Serious AKI events occurred at timepoints from the day of a device placement or replacement out to 109 days after a device replacement
  - No clear timepoint after a device placement that the risk of an AKI event substantially decreases and that could be described in the product labeling or REMS educational materials
  - Even in the setting of a clinical trial, identification of symptoms by patients and/or laboratory information by healthcare providers suggesting the device be removed was not successful at mitigating risk, with significant delays
  - Prior to experiencing an AKI event patients may experience a range of symptoms that may be mild or even absent making it difficult to identify specific labeling language that would successfully mitigate AKI risk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