FDA Briefing Document

NDA #209053

Drug name: ITCA 650 (exenatide in DUROS Device)

Applicant: Intarcia Therapeutics, Inc.

Endocrinologic and Metabolic Drugs Advisory Committee Meeting

09/21/2023

Division of Diabetes, Lipid Disorders, and Obesity (DDLO)

Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)

DISCLAIMER STATEMENT

The attached package contains background information prepared by the Center for Drug Evaluation and Research (CDER) for the panel members of the Advisory Committee.

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Glossary

AC	Advisory Committee
AE	adverse event
A1C	hemoglobin A1C (glycated hemoglobin)
AKI	acute kidney injury
ARF	acute renal failure
CAD	coronary artery disease
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
cGMP	current Good Manufacturing Practices
CI	confidence interval
CKD	chronic kidney disease
CR	complete response
CV	cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcomes trial
EOS	end of study
EOT	end of treatment
FDA	Food and Drug Administration
FDRR	Formal Dispute Resolution Request
FMQ	FDA MedDRA query
GI	gastrointestinal
GLP1RA	glucagon-like peptide-1 receptor agonist
GMP	Good Manufacturing Practices
HR	hazard ratio
IND	Investigational New Drug
IVR	in vitro release
LOCF	last observation carried forward
MACE	major adverse cardiovascular events
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction

MMRM	mixed models for repeated measures
NDA	new drug application
OCHEN	Office of Cardiology, Hematology, Endocrinology, and Nephrology
OND	Office of New Drugs
OPQ	Office of Pharmaceutical Quality
PK	pharmacokinetic
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SMQ	standardized MedDRA query
T2DM	type 2 diabetes mellitus
UA	unstable angina
WSV	within-subject variability

1 Executive Summary/Draft Points for Consideration by the Advisory Committee

1.1 Purpose/Objective of the AC Meeting

The committee will discuss the safety and efficacy of ITCA 650 (exenatide in DUROS device), a drug-device combination product submitted by Intarcia (hereafter referred to as "the Applicant") for the proposed indication "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."

1.2 Context for Issues to Be Discussed at the AC

The Center for Drug Evaluation and Research (CDER) assessed that the Applicant's New Drug Application (NDA) 209053 for ITCA 650 is not approvable in its current form because the benefit-risk assessment for the product is unfavorable based on the available data. CDER has repeatedly communicated this assessment to the Applicant and recommended in the March 9, 2020, Complete Response (CR) letter that the Applicant "redesign the product such that it provides reliable and clinically appropriate exenatide release rates over the life of the product" and "conduct new clinical trials to demonstrate the efficacy and safety of the redesigned drug-device combination product."

On July 29, 2022, CDER issued a Proposed Order to deny approval of the Applicant's NDA for ITCA 650 in its present form based on numerous deficiencies identified by CDER and discussed in detail below. Thereafter, the Applicant requested a public hearing before an advisory committee as a result of CDER's proposal to refuse approval of the Applicant's NDA for ITCA 650. CDER is holding this EMDAC meeting pursuant to a March 24, 2023, letter from the Food and Drug Administration's (FDA) Chief Scientist, Dr. Namandjé N. Bumpus, wherein she granted the Applicant's request under 21 CFR 12.32(b)(3)(ii) for a public hearing before an advisory committee in lieu of a formal evidentiary hearing regarding whether the Applicant's NDA should be approved. See Section 2.3 and Section 5.3 for a full description of the deficiencies and the regulatory background.

The Chief Scientist indicated in a February 7, 2023, letter that she will make the final decision for the Agency regarding whether the Applicant's NDA should be approved, based on the public record, including the presentations at this advisory committee meeting and the Advisory Committee's advice and recommendations, and the study data incorporated by reference in Intarcia's submissions under 21 CFR 314.200(c)(1).

1.3 Summary of CDER's Review of the ITCA 650 NDA

ITCA 650 (exenatide in DUROS device) was developed by the Applicant for the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM). ITCA 650 is a subcutaneously implanted drug-device combination product containing an osmotic mini-pump that is intended to provide a consistent daily dose of exenatide over the life of the implant. Exenatide is a glucagon-like peptide 1 receptor agonist (GLP1RA) used to improve glycemic control in patients with T2DM and contained in two FDA approved drug products.

The Applicant's proposed dosing regimen is for a patient to receive an implant of an ITCA 650 device intended to deliver an exenatide dose of 20 mcg/day for 3 months (initiation dose), followed by removal and replacement with a device intended to deliver an exenatide dose of 60 mcg/day every 6 months thereafter (maintenance dose).

In the ITCA 650 Phase 3 glycemic control trials, a statistically significant effect on reduction in A1C was demonstrated. Based on CDER's analysis, ITCA 650's treatment effect is approximately a 0.7% reduction in

hemoglobin A1C (A1C) versus placebo which is considered clinically meaningful. ITCA 650's implantable device potentially offers a method to deliver drug that is different from other approved GLP1RA products, which are given by either injection (daily or weekly) or by mouth. The Applicant has stated that this feature of ITCA 650 will improve patient adherence over weekly injectable GLP1RA products. In benefit-risk considerations, however, the potential for improved adherence among individuals who might prefer biannual medical procedures versus once weekly self-administered injections needs to be balanced against any additional risks associated with the drug, especially because evidence that an implantable device for the treatment of T2DM will translate into enhanced improvement in long-term outcomes versus injectable treatments is lacking.

CDER identified significant clinical safety concerns during review of the clinical trial data submitted to the NDA, including imbalances in adverse events (AEs) of acute kidney injury (AKI), in major adverse cardiovascular events (MACE), in serious adverse events (SAEs) and in all-cause mortality unfavorable to ITCA 650. Deficiencies in device performance were also identified that would be expected to result in inconsistent exenatide release from the ITCA 650 device in vivo. Examination of the available pharmacokinetic (PK) data showed that in some cases exenatide concentrations were markedly variable, with rapid increases, at times reaching high concentrations. The device issues, along with the finding of variable PK with rapid fluctuations, and clinical safety concerns raise significant uncertainties about the benefit risk profile of ITCA 650. These issues are summarized below and discussed in detail in Section 3.

Establishing reliable drug delivery is critical for a drug-device product intended to provide stable steady-state concentrations of exenatide for the duration of device placement. To measure exenatide release rates from ITCA 650, the Applicant used in vitro release (IVR) testing. The IVR studies, conducted under simulated use conditions in a controlled environment, demonstrated that the ITCA 650 drug-device combination product does not provide consistent and predictable release of exenatide. The data from the IVR studies showed that even after the devices reached "steady state" there were observed daily fluctuations leading in some instances to a 180% increase in dose on one day followed by a 60% decrease the next day after 4 months of study initiation. Another issue is that the Applicant proposed IVR acceptance criteria as wide as 2 to 120 mcg/day (i.e., 3% to 200% of the intended dose) but did not provide adequate justification for them and instead proposed to rely on clinical data generated in the ITCA 650 development program to retrospectively demonstrate that the acceptance criteria were adequate. Moreover, the Center for Devices and Radiological Health (CDRH) review concluded that some ITCA 650 devices failed to meet even the wide acceptance criteria proposed by the Applicant.

The PK data collected in the ITCA 650 clinical program are consistent with the findings of the IVR studies, and CDER concluded that use of ITCA 650 results in exenatide exposure with large variation and no predictable pattern, sometimes with large increases in vivo. During periods when subjects should have achieved steady-state PK, inconsistent exenatide exposures were observed both in small clinical pharmacology studies that collected rich sampling over a single 24-hour period and in a substudy of a Phase 3 trial that collected PK samples on three consecutive days during three different time periods over the 6-month lifespan of the ITCA 650 60 mcg/day device. The exenatide concentrations reported in these studies were appreciably higher both on average but especially with regard to individual outliers than previously reported for approved exenatide products. While the bioanalytical assay for exenatide concentrations differed among development programs, validated bioanalytical assays were employed. The ITCA 650 development program did not include any head-to-head data comparing the PK of ITCA 650 and Bydureon (a marketed long-acting formulation of exenatide) or any interpretable-head-to-head PK data comparing ITCA 650 and Byetta (a marketed short-acting formulation of exenatide).

In the ITCA 650 phase 3 clinical program, there was an imbalance in both serious and nonserious AKI events unfavorable to ITCA 650. In the core clinical trials, CDER identified AKI events in 46 of 2488 subjects (1.8%) who received ITCA 650 compared to 25 of 2493 subjects (1.0%) who received placebo or active comparator. Serious AKI events were reported in 14 subjects (0.56%) who received ITCA 650 versus 4 subjects (0.16%) who received comparator; 11 of 14 subjects for whom AKI SAEs were reported in the ITCA 650 treatment arm experienced GI AEs preceding the SAE. Review of the death narratives for two subjects who received ITCA 650 and were reported as having a nonserious AKI event indicated that the subjects were experiencing AKI and GI symptoms at the time of their deaths. CDER therefore considers the actual imbalance in serious AKI events to be 16 subjects (0.64%) versus 4 subjects (0.16%). Because 74 of the 79 total AKI events identified using the Applicant's search strategy were observed in FREEDOM, the cardiovascular outcomes trial (CVOT), CDER applied the Applicant's search strategy and also several alternative case ascertainment strategies to the data for FREEDOM and other GLP1RA CVOTs. CDER applied both "On-Treatment" and "On-Study" censoring strategies to calculate hazard ratios for AKI for ITCA 650 and the other GLP1RAs. A safety signal was observed for each case ascertainment strategy and each censoring strategy for ITCA 650; no safety signals were seen for any of the same hazard ratio (HR) analyses for any other GLP1RA. Time-to-event analyses for the outcome of serious and nonserious AKI for all other marketed GLP1RA CVOTs were also conducted: only FREEDOM had an appreciable imbalance in AKI. FREEDOM showed early separation of time-to-event curves that continued to separate throughout the trial.

Previous GLP1RA CVOTs have all provided a high level of reassurance regarding cardiovascular (CV) safety for the class; all of the previous CVOTs for long acting GLP1RAs have had a favorable HR for MACE and three (LEADER, SUSTAIN-6, and REWIND) supported indications for reducing the risk of MACE in patients with T2D and established CV disease (CVD) and/or risk factors for CVD. In EXSCEL, the CVOT for a marketed long-acting formulation of exenatide (Bydureon), the HR for 3-point MACE (CV death, nonfatal myocardial infarction (MI), or nonfatal stroke) was 0.91 (95% confidence interval [CI]: 0.83, 1.0). In contrast, all prespecified analyses of the MACE data from the ITCA 650 clinical development program had a HR >1. These analyses include both the 3-point MACE composite and a 4-point MACE composite (CV death, nonfatal MI, nonfatal stroke, or unstable angina (UA)), as well as the individual components of these MACE endpoints. In addition, all MACE analyses used multiple censoring strategies ("On-Study", "On-Treatment + 30 days", "On-Treatment"). The analyses were conducted for the ITCA 650 CVOT (FREEDOM) alone and on pooled MACE data from FREEDOM and the phase 3 glycemic control trials. The range of HRs include HR=1.12 (95% CI: 0.84, 1.50) for the pooled analysis of 4-point MACE using "On-Study" censoring, HR=1.24 (95% CI: 0.9, 1.70) for the FREEDOM analysis of 3-point MACE using "On-Study" censoring, HR=1.36 (95% CI: 0.96, 1.92) for the FREEDOM analysis of 3-point MACE using "On-Treatment" censoring, to HR=1.50 (95% CI: 0.82, 2.73) for the FREEDOM analysis of the individual endpoint of CV death. Each of these prespecified MACE analyses has its strengths and limitations but are consistently unfavorable. A meta-analysis conducted by CDER and a similar meta-analysis published in a peer-reviewed journal (Lee et al. 2022) using "On-Study" censoring and the 3-point MACE data from eight completed GLP1RA CVOTs including FREEDOM led CDER to conclude that the result for ITCA 650 in FREEDOM is an outlier based on a statistical comparison with other CVOTs.

The safety data from FREEDOM also showed imbalances in all-cause mortality and all SAEs not favoring ITCA 650. Deaths in FREEDOM were imbalanced (49 versus 40) not in favor of ITCA 650. In contrast, the published meta-analysis of the same CVOTs, excluding FREEDOM, demonstrated that the GLP1RA products have a favorable effect on all-cause mortality (HR 0.89 (0.83 to 0.95) (Lee et al. 2022). In FREEDOM, SAEs were observed more commonly among subjects treated with ITCA 650 (369 events) than with placebo (324 events).

Statistical analyses yielded a HR of 1.17 (1.02 to 1.39) using "On-Study" censoring. For approved GLP1RAs, the distribution of all SAEs was either balanced evenly across treatment arms or trended favorably.

CDER acknowledges that the active ingredient in ITCA 650, exenatide, is the same active ingredient in approved antidiabetic therapies. However, the ITCA 650 safety analyses along with the inconsistent device performance and the variable PK may indicate that the inconsistency in delivered dose is contributing to an unexpectedly unfavorable safety profile for a drug that otherwise has not been associated with these safety findings. During two NDA review cycles and three formal disputes, CDER concluded that the benefit-risk assessment for the ITCA 650 drug-device combination product is unfavorable. CDER weighed the benefit of improved glycemic control, considered in the context of the current therapeutic landscape for T2DM and the potential for improved adherence with the implanted device, against the risks of the product identified in CDER's review of available data from the clinical development program. The ITCA 650 development program, although having sufficiently established A1C-lowering effectiveness, has not provided sufficient reassurance of safety, emphasized by the disparate safety findings in this program compared to the programs of all other GLP1RA drugs. With respect to the risks identified, risk mitigation interventions through product labeling or a Risk Evaluation and Mitigation Strategy (REMS) could not be identified that would ensure the benefits outweigh the risks of ITCA 650. CDER continues to conclude that the unfavorable imbalances in AKI, MACE, SAEs, and all-cause mortality comprise important safety signals that must be addressed with additional clinical data before ITCA 650 can be considered for approval.

In addition, the Office of Pharmaceutical Quality (OPQ) review identified deficiencies with manufacturing controls related to the viscous drug product formulation. Due to its viscosity, certain in-process controls (e.g., equipment controls) and adequate in-process tests are necessary during manufacturing (e.g., content uniformity, visual inspection) to confirm that the drug is uniformly distributed in the formulation, is consistently and uniformly filled into the device, and that empty or improperly filled units are identified. CDER determined that in-process controls were inadequately implemented and that there was insufficient information to confirm filling uniformity for the ITCA 650 drug formulation across a batch. These deficiencies, along with additional deficiencies regarding manufacturing processes, the manufacturing facility's compliance with Current Good Manufacturing Practices (cGMP) requirements and readiness to manufacture the drug, as well as inadequate information to support the assurance of sterility for the drug product, were communicated to the Applicant and manufacturing facility across both review cycles. These deficiencies remain unresolved. However, for the purpose of the hearing, the quality deficiencies are not being presented for the Advisory Committee's deliberation. Finally, due to sterility testing results demonstrating that two lots of ITCA 650 were not sterile, Investigational New Drug (IND) application 102105 was placed on Full Clinical Hold on September 21, 2017, and all ongoing clinical studies were halted. The IND remains on Full Clinical Hold at the time of drafting this Briefing Document.

1.4 Draft Points for Consideration for the AC

- 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:
  - with respect to renal safety
  - with respect to CV safety
  - with respect to overall safety

- Discuss your assessment of the benefit risk balance of ITCA 650 for the indication to improve glycemic control in patients with T2DM.

2 Introduction and Background

2.1 Background of the Condition/Standard of Clinical Care

Diabetes mellitus is a chronic disease characterized by insulin deficiency or insulin resistance, resulting in hyperglycemia. Traditionally two major forms of diabetes have been recognized: type 1 diabetes mellitus, formerly known as insulin-dependent diabetes, resulting from reduced endogenous insulin secretion by the pancreas via autoimmune destruction of pancreatic β-cells; and T2DM, formerly known as noninsulin-dependent diabetes, characterized by insulin resistance and progressive loss of β-cell function over time. In the United States, an estimated 37.3 million people (11.3% of the population) have diabetes mellitus, with T2DM comprising about 90 to 95% of cases. An additional estimated 96 million people (38% of the population) have prediabetes based on their fasting glucose or A1C levels. Racial, ethnic, and geographic differences in diabetes prevalence are notable, with American Indians/Alaska Natives, Black and Hispanic Americans disproportionately affected, along with Americans living in the South, Midwest, and Puerto Rico (U.S Department of Health and Human Services 2020).

Depending on diabetes type and chronicity, the initial clinical presentation may vary from acute symptoms of hyperglycemia (i.e., polyuria, polydipsia, diabetic ketoacidosis) to diagnosis based on clinical screening tests in an asymptomatic patient. Due to chronic hyperglycemia resulting from diabetes mellitus, all patients are at increased risk of microvascular (i.e., retinopathy, nephropathy, peripheral neuropathy) and macrovascular (i.e., MI, stroke) complications. Large long-term randomized clinical trials such as the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) in patients with type 1 diabetes mellitus and the United Kingdom Prospective Diabetes Study (UKPDS) in patients with T2DM have demonstrated that intensive glycemic control, measured by A1C, reduces the incidence of microvascular complications (Nathan et al. 1993; UK Prospective Diabetes Study (UKPDS) Group 1998; Martin et al. 2014; Lachin et al. 2015).

Patients with T2DM have a range of therapeutic options available if lifestyle interventions fail to adequately control their dysglycemia; despite these options, up to half of patients fail to meet glycemic goals, and T2DM remains an area of unmet clinical need in the United States. In recent years, novel therapeutic drug classes that improve glycemic control without the hypoglycemia and weight gain associated with insulin have been added to the diabetes armamentarium and have supplanted older therapies in professional society clinical guidelines (Davies et al. 2022). Thirteen classes of drugs have been approved for treatment of T2DM. Among these are the GLP1RA class: eight GLP1RA products are currently marketed, and three long-acting GLP1RAs have labeled indications for benefits beyond glycemic control, such as reduction in certain CV risks (Table 1).

The 2022 American Diabetes Association/European Association for the Study of Diabetes consensus report on management of hyperglycemia in T2DM recommends a holistic person-centered approach to T2DM management, with a focus on individualized and personalized management, weight reduction, and other lifestyle interventions. Prior American Diabetes Association/European Association for the Study of Diabetes treatment guidelines recommended initiation of metformin as first-line pharmacotherapy; the most recent guidelines now recommend initiation of therapy based on the presence or absence of established CV disease or chronic kidney disease (CKD) (Davies et al. 2022). These recommendations are informed by data from large CV outcome trials and renal outcome trials, reflected in additional indications for reduction in MACE, hospitalization

for heart failure, and renal events in adults with T2DM for the SGLT2 inhibitors and GLP1RAs that have established benefit(s) beyond glycemic control.

Clinical treatment guidelines also recognize the crucial role of patient behaviors and preferences, including adherence to medications, in the management of T2DM. Adherence is defined by the World Health Organization as "the extent to which a person's behavior – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health-care provider" (World Health Organization 2003). Medication adherence is a critical clinical issue, with nonadherence leading to suboptimal glycemic control and increased risk of diabetes complications, mortality, and increased healthcare utilization including hospitalizations (Egede et al. 2014; Polonsky and Henry 2016; Khunti et al. 2017). A recent meta-analysis of seven studies evaluating 75,159 patients with T2DM taking various injectable GLP1RAs over a 6 to 12-month time period reported that once weekly GLP1RA dosing with dulaglutide, albiglutide, or exenatide extended-release was associated with higher medication adherence compared with once-daily dosing with liraglutide (Weeda et al. 2021). Nonetheless, additional therapeutic options for T2DM that are safe, effective, and improve adherence are needed.

GLP1 is an endogenous incretin hormone with receptors in the pancreas, gastrointestinal (GI) tract, brain, heart, and kidneys (Müller et al. 2019). At elevated glucose levels, GLP1 stimulates insulin secretion; GLP1 also decreases glucagon secretion and decreases appetite, leading to decreased caloric intake (Müller et al. 2019). Because of its 2-minute half-life, endogenous GLP1 itself is not suitable for use as a therapeutic agent; however, to date multiple GLP1RAs that can provide longer exposure have been developed and approved for use in the United States, including Byetta (exenatide), Bydureon (exenatide), Adlyxin (lixisenatide), Victoza (liraglutide), Ozempic (semaglutide), Rybelsus (semaglutide), Trulicity (dulaglutide) and Tanzeum (albiglutide) (Nauck et al. 2021). Table 1 lists approved GLP1RA therapies. The most recent addition to the pharmacologic armamentarium is Mounjaro (tirzepatide), a dual GLP1/glucose-dependent insulinotropic polypeptide receptor agonist (Rosenstock et al. 2021).

Table 1. Approved GLP1RA Products to Improve Glycemic Control in Adults With T2DM

Product	Available Doses	Dosing Regimen: Frequency and Route	Other Approved Indications in Adults
Byetta (exenatide immediate release)	5 mcg; 10 mcg	Twice daily subcutaneously	
Bydureon (exenatide extended-release)	2 mg	Once weekly subcutaneously	
Trulicity (dulaglutide)	0.75 mg; 1.5 mg; 3 mg; 4.5 mg	Once weekly subcutaneously	To reduce the risk of MACE in adults with T2DM and established CVD or multiple CV risk factors.
Ozempic (semaglutide injection)	0.25 mg; 0.5 mg; 1 mg; 2 mg	Once weekly subcutaneously	To reduce the risk of MACE in adults with T2DM and established CVD.
Rybelsus (semaglutide oral tablet)	3 mg; 7 mg; 14 mg	Once daily orally	
Victoza (liraglutide)	0.6 mg; 1.2 mg; 1.8 mg	Once daily subcutaneously	To reduce the risk of MACE in adults with T2DM and established CVD.
Adlyxin (lixisenatide)*	10 mcg; 20 mcg	Once daily subcutaneously	
Tanzeum (albiglutide)*	30 mg; 50 mg	Once weekly subcutaneously	

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

GLP1RA products are generally characterized by robust efficacy (as measured by improvement in glycemic control), and most GLP1RA products are also associated with body weight loss (Drucker et al. 2008; Blevins et al. 2011; Buse et al. 2013; Ji et al. 2013; Rosenstock et al. 2013; Pratley et al. 2014; Wysham et al. 2014; Ahmann et al. 2018; Pratley et al. 2019).

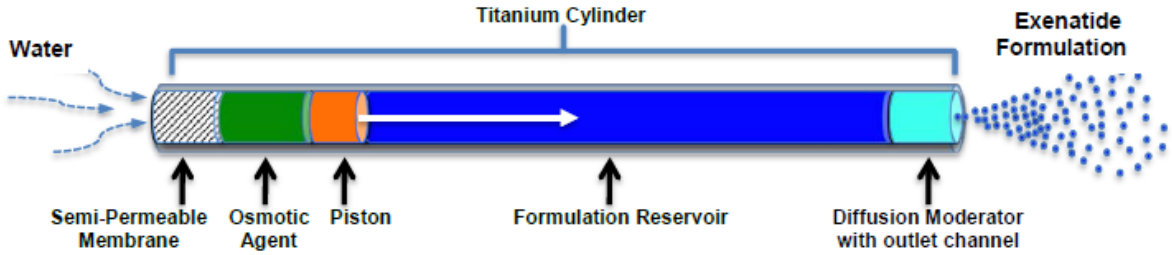
Several GLP1RA products demonstrated a statistically significant benefit on reducing MACE in cardiovascular outcomes trials (CVOTs) (Marso et al. 2016a; Marso et al. 2016b; Hernandez et al. 2018; Gerstein et al. 2019). CVOTs for several other GLP1RA products have seen HRs below 1.0 but not reaching statistical significance, for their primary MACE endpoint (Holman et al. 2017; Husain et al. 2019). ELIXA, the CVOT for Adlyxin (lixisenatide), showed no effect on MACE (Pfeffer et al. 2015); potential reasons for this include once daily dosing of lixisenatide, despite its half-life of approximately 3 hours, and differences in the ELIXA study population (i.e., subjects with T2DM and recent history of acute coronary syndrome) compared with the study populations of the other GLP1RA CVOTs (i.e., subjects with T2DM and established CVD and/or risk factors for CVD) (Nauck and Meier 2019; Nauck et al. 2021). To date, in the United States, Victoza (liraglutide), Ozempic (semaglutide), and Trulicity (dulaglutide) have been granted indications to reduce the risk of MACE in patients with T2DM at high risk of CV events.

The most common adverse reactions associated with use of approved GLP1RA products relate to GI tolerability (e.g., nausea, vomiting, diarrhea). The dosing schedule for GLP1RAs, including exenatide-containing products, generally includes a titration period of several weeks intended to gradually escalate exposures to mitigate GI tolerability issues. Conversely, sudden, large increases in exposure to a GLP1RA can cause GI adverse reactions (Fineman et al. 2004).

2.2 Description of the Drug-Device Combination Product (ITCA 650) in NDA 209053

ITCA 650 was developed by the Applicant for the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with T2DM. ITCA 650 (exenatide in DUROS device) is a drug-device combination product. It consists of a subdermal implantable device containing a mini-osmotic pump. The proposed recommended ITCA 650 dosing regimen is an initiation dose with a device stated to deliver 20 mcg/day of exenatide for 3 months, followed by titration to a maintenance dose with a device stated to deliver 60 mcg/day of exenatide every 6 months. Principal components of the device include a polyurethane membrane, osmotic agent, piston, reservoir and a diffusion moderator with channel for drug delivery (Figure 1). Per the Applicant, water from the interstitial fluid enters the mini-pump by diffusing through the semipermeable membrane. The osmotic agent, consisting of two salt tablets and filler compounds, expands as a result of the water uptake. This osmotic pressure is stated to provide the driving force to move the piston, causing drug elution from the device. The Applicant states that dose accuracy is controlled by the water uptake characteristics of the membrane, the osmotic pressure gradient between the osmotic agent and the surrounding tissue, and the concentration of drug in the drug formulation.

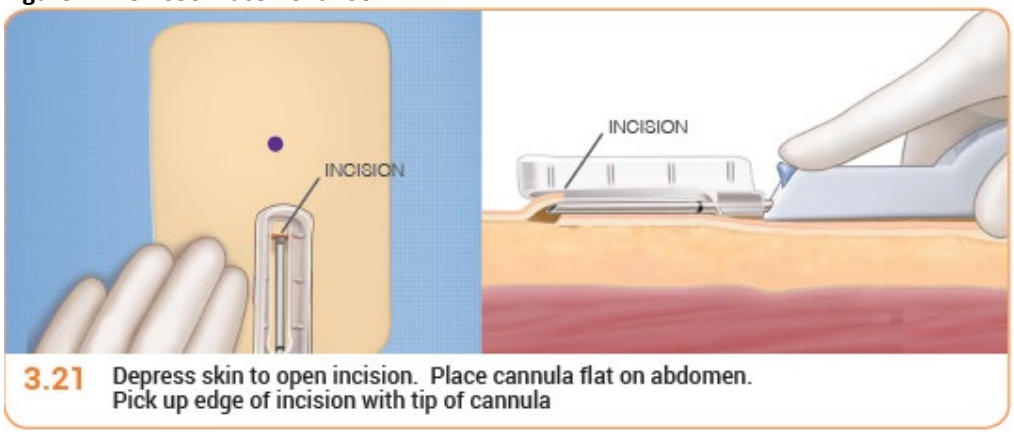
Figure 1. Cross-Sectional Diagram of ITCA 650 (Not to Scale)



Source: NDA 209053 (Seq. 0059), Description and Composition of the Drug Product, Module 3.2.P.1, p. 3.
Abbreviation: ITCA 650, exenatide in DUROS device

Exenatide is a GLP1RA used to improve glycemic control in patients with T2DM. Currently approved exenatide formulations are Byetta, injected subcutaneously twice daily, and Bydureon, injected subcutaneously once weekly. ITCA 650 uses a different exenatide formulation than the approved products: ITCA 650 contains a viscous, anhydrous suspension of spray-dried exenatide powder, citrate buffer salts, methionine, and sucrose in benzyl benzoate and povidone. The formulation is placed into the DUROS device and implanted subcutaneously in the abdomen by a healthcare professional trained in the procedure (Figure 2). To remove ITCA 650, a healthcare professional ascertains the location of the device via palpation and makes an incision through which to grasp the device with forceps and extract it.

Figure 2. ITCA 650 Placement Tool



Source: Draft Instructions for Use, p. 10, NDA 209053, SDN 0059.
Abbreviation: ITCA 650, exenatide in DUROS device

The DUROS device was approved for delivering leuprolide acetate to treat advanced prostate cancer (previously marketed under the tradename Viadur). Viadur utilized a dimethyl sulfoxide-based solution with markedly lower viscosity than the exenatide suspension used in ITCA 650. Early trials also showed that high leuprolide doses of up to 20 mg/day for 2 years did not cause different adverse effects compared to the approved 1 mg/day dose[1].

2.3 Regulatory History

2.3.1 Specific Deficiencies Identified in NDA 209053 (IND 102105)

The Applicant conducted the clinical trials for this drug development program under IND 102105 and submitted NDA 209053 on November 15, 2016. (Additional information about the pre-NDA history is provided in Table 34.) CDER issued a CR letter on September 21, 2017, for numerous deficiencies. Major clinical deficiencies listed in the CR letter included imbalances in acute kidney injury (AKI) and serious AKI events, and MACE. Other major deficiencies included failure to demonstrate consistent daily release of drug product from the device and product quality deficiencies. Major GMP deficiencies were observed in manufacturing site inspections.

The Applicant resubmitted NDA 209053 on September 9, 2019. CDER issued a CR letter on March 9, 2020, due to the major clinical, device, and cGMP deficiencies. As a path forward, CDER recommended: "To address the clinical deficiencies, you should address all the major device and product quality related deficiencies below and provide additional clinical data that adequately address the above clinical risks and establish that ITCA 650 is safe and effective for the intended use. Based on the findings of the device review and the product quality review, we recommend that you redesign the product such that it provides reliable and clinically appropriate exenatide release rates over the life of the product and that you conduct new clinical trials to demonstrate the efficacy and safety of the redesigned drug-device combination product."

Also, prior to the first CR letter, on September 18, 2017, the Applicant notified CDER of unexpected out of specification results for sterility during routine testing: *Bacillus pumus* and *Bacillus paralichiformus* were identified in two ITCA product lots. Due to these sterility testing results demonstrating the two lots of ITCA 650 were not sterile, Investigational New Drug (IND) application 102105 was placed on Full Clinical Hold on

[1] See Lupron labeling: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/019010s041lbl.pdf.

September 21, 2017, and all ongoing clinical studies were halted. The IND remains on Full Clinical Hold at the time of drafting this Briefing Document.

2.3.2 CDER's Denial of the Applicant's Formal Dispute Resolution Requests

The Applicant submitted a formal dispute resolution request (FDRR) on June 5, 2020, concerning the CR letter issued on March 9, 2020, by the former DMEP. Dr. Ellis Unger, then-Director of the Office of New Drugs' (OND) Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN), denied the FDRR on behalf of OCHEN by correspondence dated July 30, 2020, based on his determination that the risks associated with the product's unexpected numeric imbalance in cases of serious AKI, the MACE imbalance observed in the CVOT, and device-related deficiencies regarding exenatide release rates over the life of the product outweigh the benefit in reduction in A1C.

The Applicant submitted another FDRR on August 14, 2020, for review of the OCHEN denial. Dr. Robert Temple, Senior Advisor to OND, denied the second FDRR on behalf of OND by correspondence dated October 30, 2020, based on his determination that the product's clinical risks, device-related deficiencies, and product quality and manufacturing deficiencies had not been satisfactorily resolved, reaffirming the reasoning in OCHEN's denial of the prior FDRR.

The Applicant submitted a third FDRR on November 27, 2020, for review of the OND denial and requested an advisory committee meeting. Dr. Douglas Throckmorton, Deputy Director for Regulatory Programs, CDER, denied the third FDRR and the request for an advisory committee meeting on behalf of CDER by correspondence dated February 12, 2021, based on his determination that the product's clinical risks and device-related deficiencies had not been satisfactorily resolved. Dr. Throckmorton reaffirmed the reasoning in OND's denial of the prior FDRR and concluded that an advisory committee would be premature because of foundational scientific issues and substantial unresolved deficiencies requiring additional data. Dr. Throckmorton's denial letter stated: "For this application, the central disagreement appears to be that the FDA believes additional data, both clinical and in vitro, are needed to resolve uncertainties before approval can be contemplated, and you believe otherwise. As outlined in the CR letters and summarized above and in the appeal denial letters from Drs. Unger and Temple, I agree that these deficiencies are substantial. I conclude that they are substantial enough that an AC recommendation would not alter the need for the uncertainties to be addressed preapproval... In the end, there are foundational scientific issues that FDA staff have identified that would not benefit from an AC discussion at this time."

2.3.3 The Applicant's Hearing Request

On March 16, 2021, the Applicant submitted a request under 21 CFR 314.110(b)(3) for an opportunity for a hearing on whether there are grounds under section 505(d) of the FD&C Act for denying approval of NDA 209053.

In the Federal Register of September 2, 2021, CDER published a Notice of Opportunity for a Hearing regarding CDER's proposal to refuse to approve NDA 209053. 86 Fed. Reg. 49,334. The Notice of Opportunity for a Hearing gave the Applicant an opportunity to request a hearing before the Commissioner of Food and Drugs (the Commissioner) on CDER's proposal to refuse to approve NDA 209053. On September 13, 2021, the Applicant submitted a notice of participation and request for a hearing. The Applicant submitted data, information, and analyses in support of its hearing request on November 1, 2021, and February 15, 2022.

On July 29, 2022, CDER issued, via email to the Applicant, a Proposed Order proposing to refuse to approve NDA 209053 in its present form. See Docket FDA-2021-N-0874. The Applicant responded to CDER's Proposed Order on October 10, 2022.

On February 7, 2023, the Chief Scientist of FDA, Dr. Namandjé N. Bumpus, issued a letter to the Applicant and CDER that stated, in part: "Under 21 CFR 12.32(a), a person seeking a hearing under 21 CFR part 12 may request an alternative form of hearing, such as a hearing before a public advisory committee under 21 CFR part 14." Dr. Bumpus stated that she would grant the Applicant's request for an alternative form of hearing under 21 CFR part 14 in lieu of a formal evidentiary hearing under 21 CFR part 12. On February 20, 2023, the Applicant submitted a request in the form of a citizen petition, requesting a public hearing before an advisory committee under 21 CFR part 14 in lieu of the Applicant's pending request for a formal evidentiary hearing under 21 CFR part 12. In accordance with 21 CFR 12.32(b)(3)(ii), the Applicant waived its right to request a formal evidentiary hearing under 21 CFR part 12. On March 24, 2023, Dr. Bumpus issued a letter granting the Applicant's request for an alternative form of hearing.

CDER is holding this meeting pursuant to the March 24, 2023, letter from Dr. Bumpus, wherein she granted the Applicant's request under 21 CFR 12.32(b)(3)(ii) for a public hearing before an advisory committee in lieu of a formal evidentiary hearing. In that letter, Dr. Bumpus stated that she was "refer[ring] the matter to CDER to conduct the [public hearing before the advisory committee] consistent with [CDER's] typical process under 21 CFR part 14." In light of this instruction, CDER is holding this meeting following the same process it utilizes for its other advisory committee meetings.

See Table 34 for further detail on the meetings between the Applicant and CDER.

3 Issues for the AC

3.1 Device

3.1.1 Proposed In Vitro Release Rates for the ITCA 650 Device Constituent

ITCA 650 is intended to provide continuous dosing of exenatide from an osmotic mini-pump implanted in the subdermal space of the abdomen for 3 months from initiation of therapy, and every 6 months afterwards for maintenance therapy. ITCA 650 is proposed in two dosage strengths: 20 mcg/day for 3 months during the initiation Phase and 60 mcg/day for 6 months. The purpose of the DUROS device component is to provide consistent release of drug from the device to the patient over the duration of use.

In order to evaluate the device's ability to achieve this, the Applicant developed an in vitro assay referred to as in vitro release (IVR) testing. The IVR testing is intended to measure drug release by immersing the semipermeable membrane portion of the pump in phosphate-buffered saline and the diffusion moderator end of the pump in a release medium. The phosphate-buffered saline is intended to simulate the interstitial fluid and serves to hydrate the osmotic engine leading to the displacement of the plunger and release of drug into the release medium. Aliquots of the release medium are collected at specified intervals and the amount of drug released is quantified by reverse-phase high-pressure liquid chromatography. This method of assessing the rate of drug delivery utilizes highly controlled conditions. Additional factors that may determine actual in vivo release (e.g., hydration level of the patient and the device, local temperature at the site of delivery, local tissue fibrosis or inflammation) are not accounted for by IVR studies. Therefore, IVR studies represent an idealized test case to approximate in vivo release rates because they do not account for the expected biological sources of variability.

In the original 2016 NDA, the Applicant provided weekly and biweekly IVR data to demonstrate how the device delivers exenatide. For this study, devices were allowed to release exenatide under the above-mentioned conditions, and samples were taken on a weekly or biweekly basis. However, while weekly or biweekly IVR data may be sufficient for release or stability testing, it is insufficient to verify and validate the device design as it is not a clinically relevant delivery interval (Table 34). Given its 2 to 4-hour half-life, exenatide must administered either multiple times daily or consistently throughout the day to achieve a desirable clinical result. A demonstration that the weekly delivery rate would provide the total dose intended for the week is not adequate to conclude that clinically appropriate doses of drug are delivered each day. Furthermore, the data did not demonstrate consistent drug delivery rates throughout the intended use-life of the device or that devices would reach a "steady state" where consistent IVR was achieved. In an Information Request issued on May 1, 2017 (DARRTS Reference ID: 4092071), and in the CR letter issued on September 21, 2017, CDER requested additional IVR data to cover the entire in-use period of the device and stated that data should ensure accurate delivery to achieve the desired therapeutic effect. This was further discussed in the Type B meeting held on May 9, 2018 (DARRTS Reference ID: 4275017), and CDER expressed the need for daily IVR data for the in-use period of the device, rather than weekly or biweekly.

With the resubmission of the NDA in 2019, additional daily IVR data were provided to try to address CDER's concerns. For this study, the Applicant proposed the following acceptance criteria for drug release that vary based on the duration of testing (i.e., simulated use of the device) (Table 2).

Table 2. Daily IVR Proposed Acceptance Criteria for the 20 mcg/Day and 60 mcg/Day Products

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.
Abbreviation: IVR, in vitro release

The proposed daily IVR ranges vary based on how long the device has been in use. For the 20 mcg/day presentation, the proposed IVR range is 2 to 40 mcg/day for the first 2 weeks of use, which represents 10% to 200% of the 20 mcg/day target dose. In addition, for Weeks 3 to 13, the proposed range for this presentation is 10 to 36 mcg/day, which represents 50% to 180% of the target dose.

Similarly, for the 60 mcg/day device, the proposed daily IVR range for the first 4 weeks is 2 to 120 mcg/day, which represents 3.3% to 200% of the 60 mcg/day target dose. The proposed IVR range for the remaining weeks is 25 to 110 mcg/day, which represents 50% to 180% of the target dose.

These proposed IVR acceptance criteria for daily drug release are significantly wider than other drug delivery devices such as pen injectors and infusion devices. For example, injection products, such as pen injectors, conforming to the International Organization for Standardization (ISO) 11608-1 standard (*Needle-Based Injection System for Medical Use – Requirements and Test Methods – Part 1: Needle-based Injection Systems*) (International Organization for Standardization 2022) generally have a dose accuracy of no wider than ±5% of the intended target dose. In addition, infusion products such as on-body insulin pumps or large volume infusion pumps commonly allow for a variation of ±5 to 15% of the specified infusion rate. In contrast, the Applicant's

proposed performance criteria for ITCA 650 are as wide as -97% to +100% of the intended target daily dose of the product.

Discussion of IVR Data

The Applicant provided daily IVR data for selected intervals during days 0 to 91 for 12 units of the 20 mcg/day device (Group A) and for 24 units of the 60 mcg/day device (Groups B and C). One unit represented one filled ITCA 650 device. The 60 mcg/day devices were further divided into two subgroups of 12 units: one to measure daily IVR during selected intervals from Days 0 to 112 (Group B); and one to measure daily IVR during selected intervals from Days 112 to 182 (Group C). For each of the sample groups, testing consisted of repeating periods of daily IVR measurements followed by weekly IVR measurements. Time periods denoted as "Transfer from Weekly to Daily IVR" indicate a 2-day IVR measurement followed by daily IVR testing for the remaining days. The test schedule is shown in Table 3.

Table 3. In Vitro Release Sampling Schedule for 20 and 60 mcg/Day Devices (Study VV 5288)

		IVR Sampling Intervals (Weeks)																	
Cohort	**Dose**	**1,2,3**	**4**	**5**	**6**	**7,8**	**9**	**10**	**11**	**12**	**13**	**14**	**15,16**	**17,18**	**19**	**20,21**	**22,23**	**24**	**25,26**
Group A (N=12)	20 mcg/day	D	W	T	D	W	T	D	W	D					None				
Group B (N=12)	60 mcg/day	D	W	D	D	W	T	D	D	W	W	T	D	NS	NS	NS	NS	NS	NS
Group C (N=12)	60 mcg/day	Weekly												W	T	D	W	T	D

Source: CDER Reviewer's summary, adapted from Study VV 52888 (SDN0060), Table 1 and Table 2.
For Group B data after Day 112 (Week 16) were not included in the analysis and report for design verification per the study protocol.
Abbreviations: D, daily sampling; IVR, in vitro release; NS, not submitted; T, transfer from weekly to daily sampling; W, weekly sampling

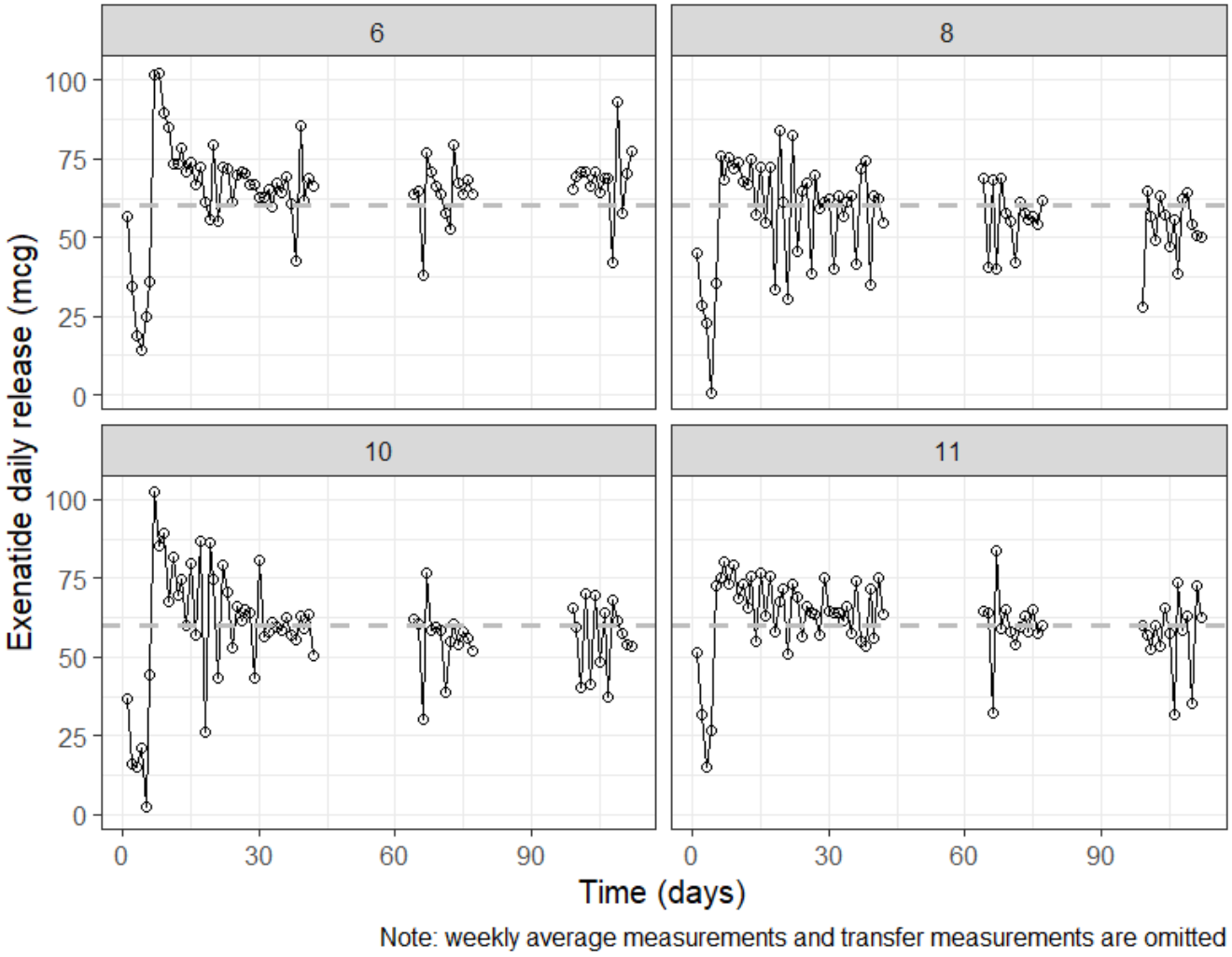
In addition to the proposed daily IVR acceptance criteria in Table 2 above, the Applicant proposed various biweekly and weekly acceptance criteria. The Applicant did not provide acceptable justifications for the proposed biweekly, weekly, and daily acceptance criteria, and instead relied on the safety and efficacy data from the clinical trials to provide support for the acceptance criteria selected. As described in Section 3.3, CDER identified significant safety concerns in review of the Phase 3 trial data.

Given the 2 to 4-hour half-life of exenatide, consistent drug delivery throughout the day is critical to achieve stable steady-state concentrations. Whether there is consistent and precise hourly drug delivery, however, cannot be confirmed based on cumulative biweekly, weekly, or daily drug delivery rates. The review team concluded that the data measuring weekly release rates provide very limited insight into whether the rate and reliability of exenatide release from the devices are clinically acceptable. CDRH therefore focused its review of the intervals during which daily IVR results were obtained.

For the 20 mcg/day presentations, the overall daily release profile was generally characterized by average low but highly variable initial release over the first 1 to 4 days. When the observed rates for all units are averaged over several days, the periods of underdelivery and overdelivery are not apparent. More relevant than the averages, however, is the variable release rates of the individual devices. For example, Unit 11A delivered 0 mcg/day exenatide over the first 2 days but delivered up to 41 mcg/day on Day 5 (note that 0 to 41 mcg/day exceeds the Applicant's acceptance criteria of 2 to 40 mcg/day for Weeks 1 to 2). At "steady state" (Weeks 3 to 13), drug delivery continued to be variable, both throughout the lifespan of a device and also between devices. For example, during this time period, Unit 10A delivered between 24 and 28 mcg/day while Unit 1A delivered between 15 and 23 mcg/day.

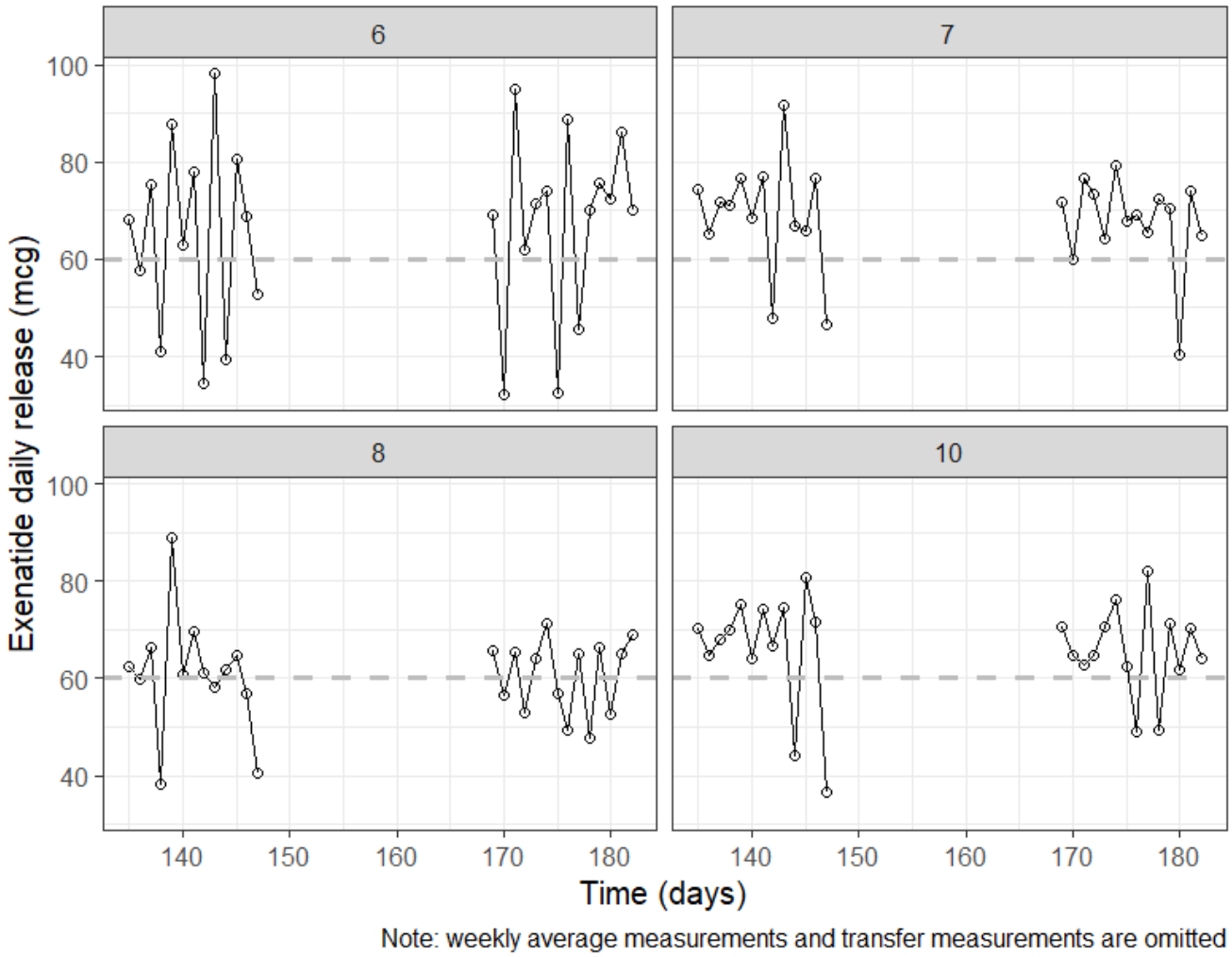
Similar to the 20 mcg/day presentation, the 60 mcg/day presentation also exhibited variable delivery performance that featured an initial period of low delivery followed by a period of high delivery. In the 60 mcg/day presentation, both the initial period of low delivery and the follow-on period of high drug delivery are extended to 1 week and 2 weeks, respectively. Daily IVR ranged from a minimum of 0 mcg/day (Unit 3B, Day 2) to a maximum of 103 mcg/day (Unit 10B, Day 7). In addition, the 60 mcg/day presentation continued to exhibit highly variable drug delivery throughout the "steady state" period (defined as Day 28 to 182 of IVR testing) of the device lifespan. Variability of individual units was highest in Unit 10B with a range of 3 to 103 mcg/day, which occurred within the first week of IVR testing, and the highest variability at "steady state" was observed in Unit 6C where delivery rates varied between 32 to 98 mcg/day. Examples of the inconsistent drug delivery by the 60 mcg/day device in the IVR studies are shown in Figure 3 and Figure 4. Figure 3 reports IVR data collected during days 0 to 112 of the device lifespan, whereas Figure 4 reports IVR data collected between Days 112 to 182 of the device lifespan. While the largest variability occurs in the 2 weeks after initiation of the study, the IVR data indicates that the 60 mcg/day presentation performs inconsistently with large day-to-day variations throughout the device's lifespan. For example, as seen in Figure 4, Unit 6C delivered 78 mcg on Day 141, 35 mcg on Day 142, 98 mcg on Day 143, 39 mcg on Day 144, and 80 mcg on Day 145. See Section 5.1 for the individual performances of all 24 units of the ITCA 650 60 mcg/day device tested, and all 12 units of the ITCA 650 20 mcg/day device tested (Figure 19, Figure 20, and Figure 21).

Figure 3. 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)



Source: CDER Review staff. Software: R v. 4.2 (IVC_plots.R); data adapted from Study VV 52888 (SDN0060).
Abbreviations: ITCA 650, exenatide in DUROS device; mcg; microgram

Figure 4. 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)



Source: CDER Review staff. Software: R v. 4.2 (IVC_plots.R); data adapted from Study VV 52888 (SDN0060).
Abbreviations: ITCA 650, exenatide in DUROS device; mcg; microgram

Consistent with the unpredictable and highly variable nature of drug release from the device, some devices released significantly higher amounts of exenatide than what would be expected based on a 60 mcg/day target drug release. For example, Unit 4B delivered 1122 mcg of exenatide in a 14-day period (Days 7 to 20), where the cumulative target dose of exenatide would be 840 mcg (60 mcg × 14 days). This represents an overdelivery of 34% of exenatide with several days where the device delivered markedly above the period average (34%).

3.1.2 Assessment of Device Reliability

ITCA 650 is an implanted device with no mechanism to communicate the drug delivery status to the user or the healthcare provider (e.g., user interface). Users will not be aware of any device malfunctions such as interruption of therapy (device occlusion), inconsistent drug delivery, or early piston stoppage. A patient may only discover that a device failure occurred during use due to the onset of symptoms related to the device failure. This lack of user awareness regarding the status of drug delivery necessitates a high degree of device reliability to ensure that use of the device is safe in patients. In this context, reliability is defined as the probability that the device will perform satisfactorily for a specified period of time for the intended use (Food

and Drug Administration 1980). As consistent drug delivery is the most important performance attribute for the DUROS device, the Applicant should demonstrate that there is a high probability that devices deliver drug within clinically acceptable specifications throughout the intended use life. Although CDER typically recommends that sponsors demonstrate that dose accuracy requirements are met with 95% confidence and 95% reliability (Advancing Safety in Health Technology (AAMI) 2021; International Organization for Standardization 2022), an even higher level of reliability is expected (>99%) for an implantable device that does not communicate device critical failures to the end user.

The Applicant identified three major failure modes for the device that would impact the device's ability to deliver the drug accurately and provided associated failure rates: piston stoppage, early exhaustion, and inconsistent formulation delivery, and reported failure rates of 0%, 0.17%, and 0.09%, respectively, based on 1170 tested units. However, the definitions used by the Applicant for device failures are inadequate to identify relevant device failure rates. For example, the Applicant defined inconsistent formulation delivery as "≥ three (3) instances where the weekly IVR rate is measured 50% above or below the target rate before completion of the in-use period." As a result, devices that performed outside of the Applicant's release specifications, on at least three separate occurrences, but were within 50% of the weekly target dose were not counted in the figures for "inconsistent delivery of formulation" (NDA 209053, ITCA 650 [exenatide in DUROS], Type A End-of-Review Meeting Minutes dated April 24, 2020 [DARRTS Reference ID: 4612424]). In addition, as detailed above, weekly assessment of IVR is not adequate to measure drug delivery for a drug with a short half-life particularly given the unpredictable delivery performance.

When assessing device reliability, any deviation from clinically acceptable drug delivery specifications should be counted as a device failure. As seen within the small daily IVR study, even though the proposed acceptance criteria already allow for significant variability and are not clinically justified, some devices still deviated from these proposed IVR ranges (e.g., Unit 11A, Unit 3B, and Unit 8B). Hence, some failures can be observed in this small study which could result in a much higher failure rate than what is reported by the Applicant.

As a result of the issues described above, the Applicant's reported failure rates represent a gross underestimation, and clinically meaningful failure rates of the device are not fully known. As stated above, the device design and intended use of the product necessitate a high degree of assurance that devices accurately deliver drug. Users may only become aware of device issues, such as dose dumping or under delivery, if they develop associated symptoms. In addition, some users may not associate symptoms with the use of the device, which can further prolong the time until the device is removed while the patient may be exposed to high, low, or variable amounts of exenatide. Given the variable IVR data and that meaningful failure rates for the device are unknown, the proposed combination product does not meet clinically relevant reliability and accuracy specifications for its intended use.

In conclusion, CDER concluded that ITCA 650 fails to deliver exenatide doses accurately and reliably. The IVR studies, conducted under simulated use conditions in a controlled environment to measure exenatide release rates, demonstrated that the ITCA 650 drug-device combination product does not provide accurate and predictable release of exenatide. The highly variable exenatide release rates suggest that use of the device may expose patients to rapid exenatide exposure excursions at unpredictable timepoints after device implantation. The Applicant proposed IVR acceptance criteria that CDER concluded were excessively wide and lacked appropriate clinical justification. Whereas the Applicant believes that the clinical data are sufficient to establish that the acceptance criteria are adequate, CDER disagrees because of unfavorable clinical safety imbalances observed (discussed in Section 3.3.2). Moreover, CDRH's review of the IVR studies concluded that some ITCA 650 devices failed to meet even the wide acceptance criteria proposed by the Applicant. In addition to high

variability in IVR testing, the Applicant has not provided adequate information to enable reasonable estimation of device failure rates.

3.2 Clinical Pharmacology

Background

The estimated release rates from the IVR studies discussed above do not account for in vivo factors (e.g., hydration level of the patient and the device, local temperature at the site of delivery, local tissue fibrosis or inflammation). For this reason, in vivo performance of the device provides important, but distinct information in assessing performance of the combination product.

Tolerability of GLP-1 receptor agonists such as exenatide, especially GI tolerability, relates both to absolute drug concentrations and rapid increases in concentrations (Fineman et al. 2004). Exenatide has the shortest half-life of all the approved GLP1RAs (~2 to 4 hours). As such, the blood drug level at any given time is particularly dependent on the exenatide release rate from the previous few hours. The findings of the IVR studies suggest the potential for wide swings in release rates and rapid increases in drug concentrations. These observations make evaluation of clinical PK with ITCA 650 particularly important.

During development of ITCA 650, the Applicant used different PK assays at different stages of development; Phase 1 Study CLP-01 and Phase 2 Study CLP-02 evaluated exenatide PK using a "Generation 1" assay, while all later studies evaluated exenatide PK using a "Generation 2" assay. In addition, manufacturing changes occurred during development, such that "Group A" device lots were utilized in early-stage studies, while late-stage studies utilized "Group B" device lots that more closely resemble the to-be-marketed lots. Finally, as detailed in the regulatory history (Section 2.3 and Table 34), during clinical development of ITCA 650 CDER raised concerns regarding higher-than-expected exenatide exposures and the high incidence of persistent nausea in Study CLP-02, and advised the Applicant that the NDA submission should contain justification for the device drug release rates.

Clinical Pharmacology Data

The PK data of ITCA 650 were obtained from studies shown in Table 4. These include PK/pharmacodynamic and dose ranging studies (CLP-01 and CLP-02), a renal impairment study (CLP-109), and drug-drug interaction studies (CLP-115 and CLP-116). Two Phase 3 studies included PK sampling: CLP-103SS, a 26-week extension ('Extension 1') substudy of CLP-103 (n=37), and CLP-203.

Only some studies provided sampling frequent enough to assess the in vivo performance of the product. CDER focused on PK data from Studies CLP-103SS, CLP-116, and CLP-109 because these studies used Group B device lots, the Generation 2 PK assay to evaluate exenatide PK, and employed frequent PK sampling. Study CLP-115 and Study CLP-203 utilized Group B lots and also collected some PK data using the "Generation 2" assay, but the PK sampling timepoints were limited and thus data did not allow for evaluation of day-to-day release variability (Table 4).

The Applicant's analyses of the PK data submitted to the NDA focused on the individual and population concentration averages, rather than how concentrations in an individual patient change over time (e.g., day-to-day variability). In addition to corroborating these analyses, CDER also evaluated the PK data observed over time for individual patients. CDER considers its investigations into the subject-level PK data important because they illustrate time periods during which some devices fail to deliver exenatide at a constant rate.

Table 4. Studies With Pharmacokinetic Information

Phase	Study	Design	PK Sampling Scheme	Device Used	Bioanalytical Assay
Phase 1	CLP-01	Dose escalating (subjects with T2DM) n=38 with observed PK	Day 1 (preplacement, 6 and 12 hours postplacement), Day 2, 3, 4, 5, 8, 15, 22, 29 (prior to and 3 hours after removal), 30 (24 hours postremoval)	20 mcg/day, 40 mcg/day*, 80 mcg/day*	Gen. 1
	CLP-109	Renal impairment n=38 with observed PK	20 mcg device: Day 1 (preplacement, 4 and 8 hours postplacement), Days 7-8; 60 mcg device; Day 1 (preplacement, 4 and 8 hours postplacement), and Days 7-8, also 2, 4, 5, and 8 hours after removal of device (Day 9, 10, or 11)	20 mcg/day, 40 mcg/day*, 60 mcg/day	Gen. 2
	CLP-115	DDI (gastric emptying with APAP + DDI probe drug cocktail) n=33 with observed PK	2, 4, 6, and 8 hours postplacement	20 mcg/day, 60 mcg/day	Gen. 2
	CLP-116	DDI with oral combination contraceptive n=27 with observed PK	Steady-state Day 14 and Day 28 (2, 4, 8, 12, 16, 24 hours). The 24-hour sample was obtained prior to removal of device on Day 15 and Day 29.	20 mcg/day, 60 mcg/day	Gen. 2
Phase 2	CLP-02	24-week dose-ranging study (subjects with T2DM) n=141 with observed PK	Weeks 1, 12, 13, 24, 48, and end of treatment + 4 weeks; Week 12 and Week 48 samples collected prior to device removal	20 mcg/day, 40 mcg/day*, 60 mcg/day	Gen. 1
Phase 3	CLP-103SS	Substudy Extensions 1, 2 and 3, the three 26-week extensions of the 39-week Phase 3 study to evaluate ITCA 650 in subjects with T2DM with high baseline A1C (with PK assessed in CLP-103SS Ext. 1) n=37 with observed PK	Weeks 41, 52, 65 (corresponding to Weeks 2, 13, and 24 postplacement most recent ITCA 650 placement; samples collected on three consecutive days each of these weeks)	60 mcg/day	Gen. 2
	CLP-203	Phase 3 randomized, active comparator, open-label, multicenter study to compare the efficacy, safety and tolerability of ITCA 650 to empagliflozin and to glimepiride as add-on therapy to metformin in subjects with T2DM. n=34 subjects had Week 13 PK data collected before the trial was halted due to the IND being placed on Full Clinical Hold.	Planned: Weeks 13, 26, 39, 52, and 65 Completed: 34 subjects had Week 13 PK data	20 mcg/day, 60 mcg/day	Gen. 2

Source: CDER Reviewer's summary.

* ITCA 650 40 mcg/day and 80 mcg/day were evaluated in the clinical development program but not proposed for marketing in the NDA submission.

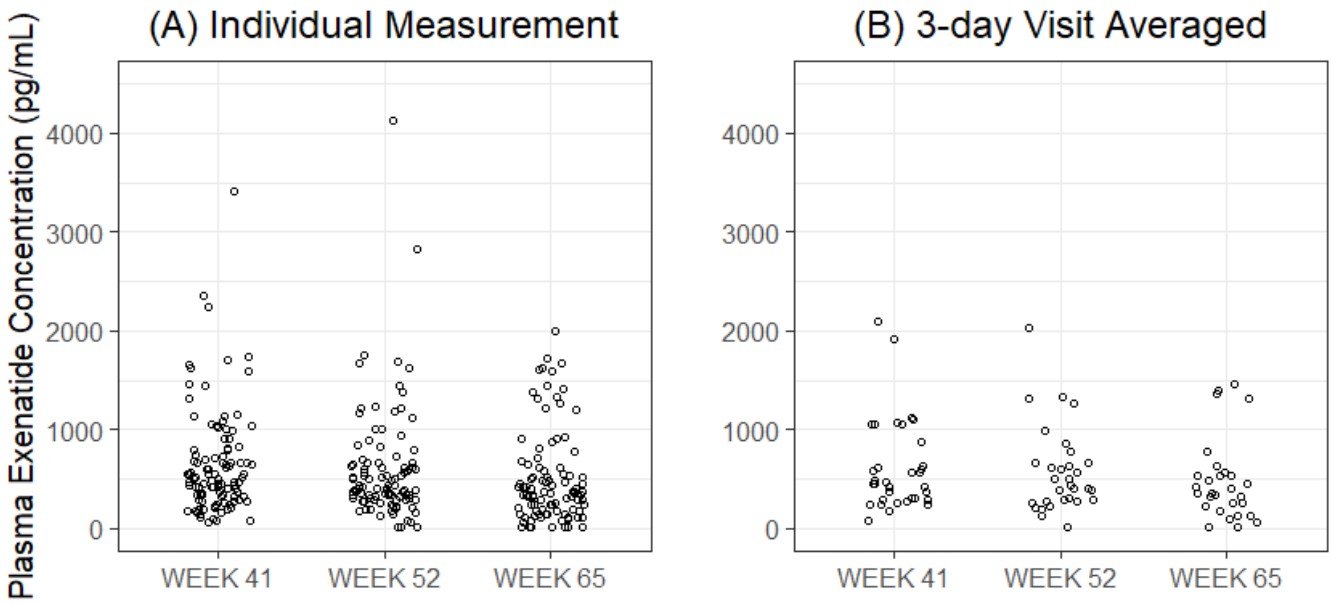
Abbreviations: APAP, acetaminophen; Hb1Ac, hemoglobin 1Ac; DDI, drug-drug interaction; ITCA 650, exenatide in DUROS device; IND, investigational new drug application; PK, pharmacokinetics; T2DM, type 2 diabetes mellitus; Gen 1, Generation 1 assay; Gen 2, Generation 2 assay

Findings From CLP-103SS

Initially, the Applicant's Phase 3 Study CLP-103 included provisions for collecting PK samples for every patient at every study visit. However, the Applicant later amended the protocol to remove the provisions for the PK sampling. For that reason, the only PK data collected in CLP-103 came from a 26-week extension ('Extension 1') of a substudy of 37 subjects (CLP-103SS) who did not meet the inclusion/exclusion criteria for CLP-103. The Phase 3 PK data from CLP-103SS are discussed in detail below, as these Phase 3 substudy data comprise the most relevant of the PK data available to assess exenatide exposures achieved with ITCA 650 over the proposed device lifespan.

Enrollment criteria for the CLP-103SS were similar to those for the main CLP-103 glycemic control trial, with the exception of baseline A1C (A1C was between 10 and 12%). Baseline A1C is not expected to affect the pharmacokinetics of ITCA-650. PK samples were collected at three visits during Week 41, Week 52, and Week 65 (i.e., 2 weeks, 13 weeks, and 26 weeks after the replacement ITCA 650 60 mcg device was placed at Week 39), timepoints selected due to the expectation that they would reflect steady state exenatide exposures. During each visit subjects had PK samples taken on three consecutive days, for a total of nine samples for each subject. In the NDA submission, the Applicant reported three-day average exenatide concentrations for each subject at each visit. Because CDER noted that averaging the PK samples collected over the three consecutive days could mask the variability of the exposures, CDER also analyzed the daily individual PK samples collected. Results of CDER's individual PK analyses reveal the extent of day-to-day intrasubject variability in exenatide exposures (Figure 6 and Figure 7) as compared with the presentation of 3-day averaged exposures (Figure 5).

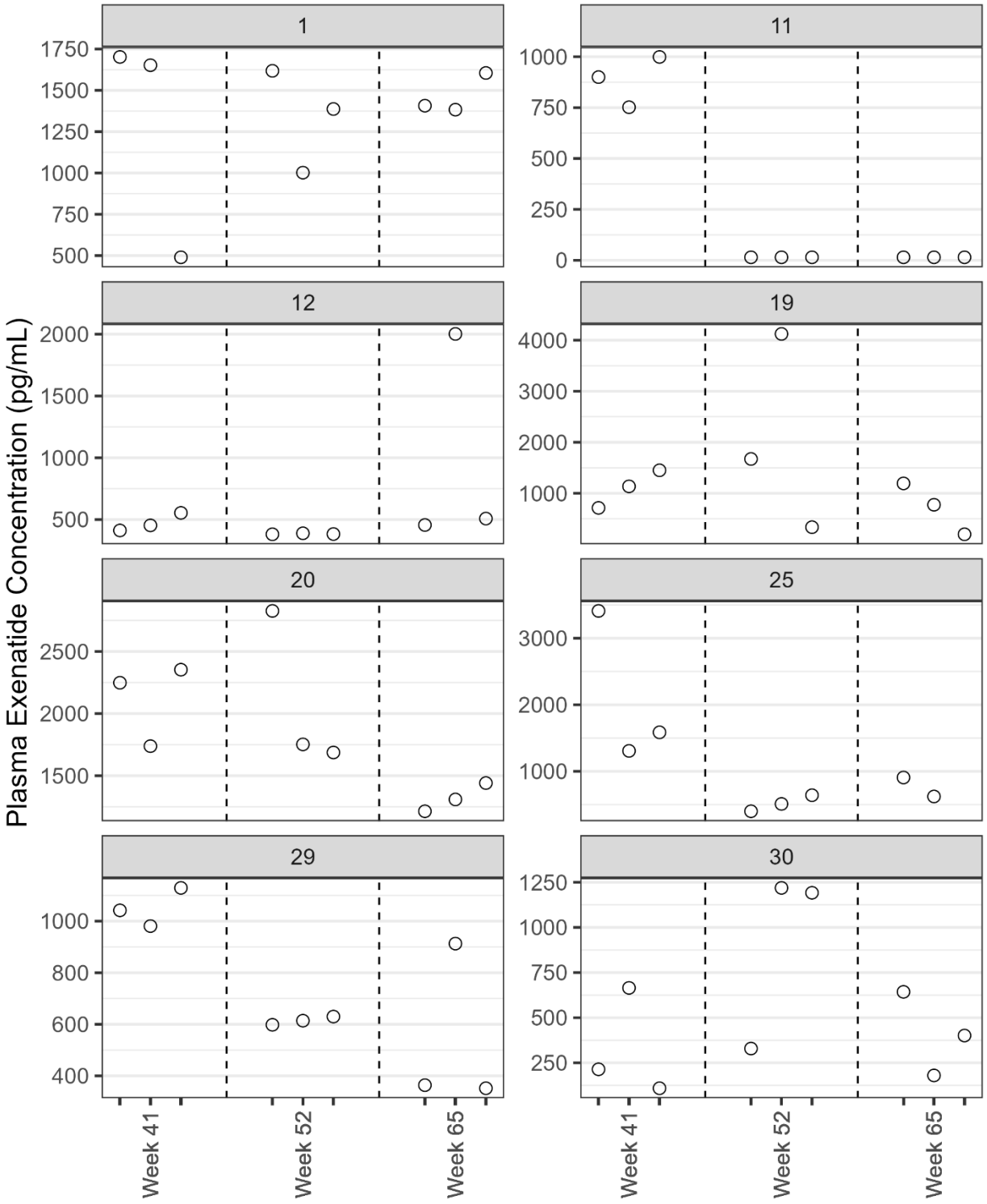
Figure 5. (Panel A) Individual PK Samples Collected on Three Consecutive Days for Subjects in CLP-103SS With the ITCA 650 60 mg Device in Place; (Panel B) 3-Day Average Exposures for Individuals in CLP-103SS With the ITCA 650 60 mg Device in Place



Source: CDER Review staff. Software: R v. 4.2 (PK_plots.R); data: adpc.xpt (SDN0000).
Results are consistent with p. 42 of the CSR for CLP-103SS First Extension Phase (SDN0000).
Abbreviations: CSR, clinical study report; ITCA 650, exenatide in DUROS device; PK, pharmacokinetics

Inspection of Figure 5 shows wide variability in exenatide exposures at the population level, and Figure 6 (which presents individual subject PK data) reveals wide intrasubject variability and demonstrates that some subjects experienced marked day-to-day changes in exenatide exposures. As noted previously, these changes in exposures occurred during time periods where steady-state exposures should have been achieved. The most plausible explanation for the extreme changes in exenatide concentrations observed in these patients during expected periods of steady-state exposure is inconsistent delivery of drug by the ITCA 650 device.

Figure 6. Variable Exenatide Exposure – Selected Subjects in Study CLP-103SS



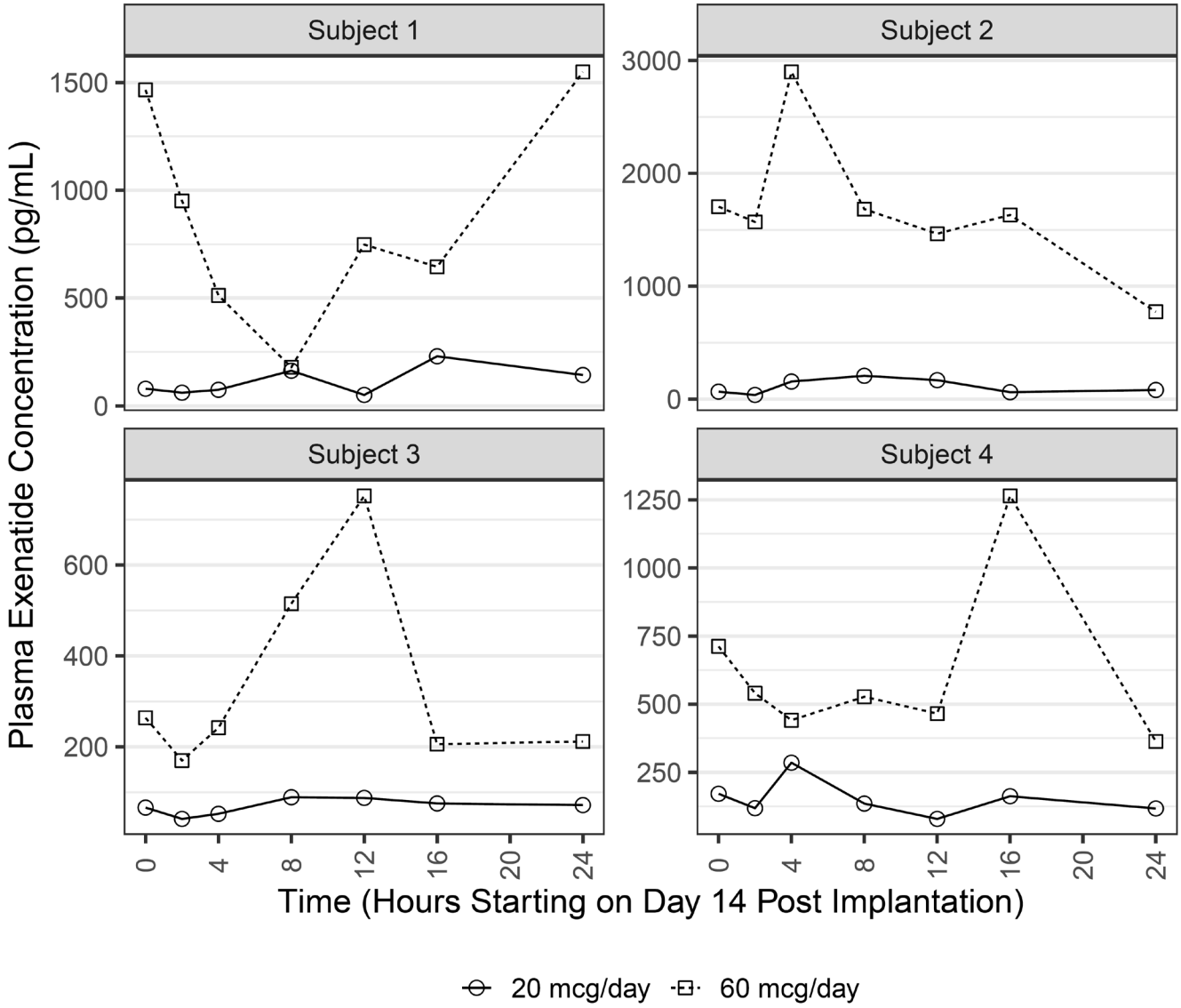
Source: CDER Review staff. Analysis: R v. 4.2. using sdtm (pc.xpt) from SDN0000.
PK values below the quantification limit are imputed as the lower limit of quantification divided by 2.
Refer to Section 5.3 for a presentation of all subjects' PK data from CLP-103SS (Figure 16).
Abbreviation: PK, pharmacokinetics

PK samples were collected only when the subject was well enough to report to scheduled clinic visits; PK samples were not collected at the time SAEs occurred such that the data are unable to definitively link supratherapeutic or rapidly increasing exenatide exposures to observed SAEs that resulted in hospitalization or death; however, the data are insufficient to exclude this possibility.

Findings From ITCA-650 Study CLP-116 and Study CLP-109

Although CDER views the PK data from CLP-103SS as the best available data to assess ITCA-650's *in vivo* performance, additional insight can be gained from Phase 1 clinical pharmacology studies in which Group B lots were used. CLP-116 collected rich sampling 2 weeks after device implantation for both the ITCA 650 20 mcg/day device and the ITCA 650 60 mcg/day device. Although CLP-116 did not collect PK data over the lifespan of the device, the PK data collected during periods of frequent sampling when steady-state concentrations should have been achieved support the conclusion that ITCA 650's delivery of exenatide is not consistent. CDER identified at least four subjects who experienced significant changes in exposures over the course of the day, despite the small sample size (n=27) and the single day of rich sampling (Figure 7). The PK exposures observed for some other subjects receiving the 60 mcg/day device during the period of frequent PK sampling exhibited less dramatic excursions. However, the conclusion that the ITCA 650 device sometimes performs inconsistently is not at odds with data suggesting the ITCA 650 device sometimes performs as intended over short periods of time.

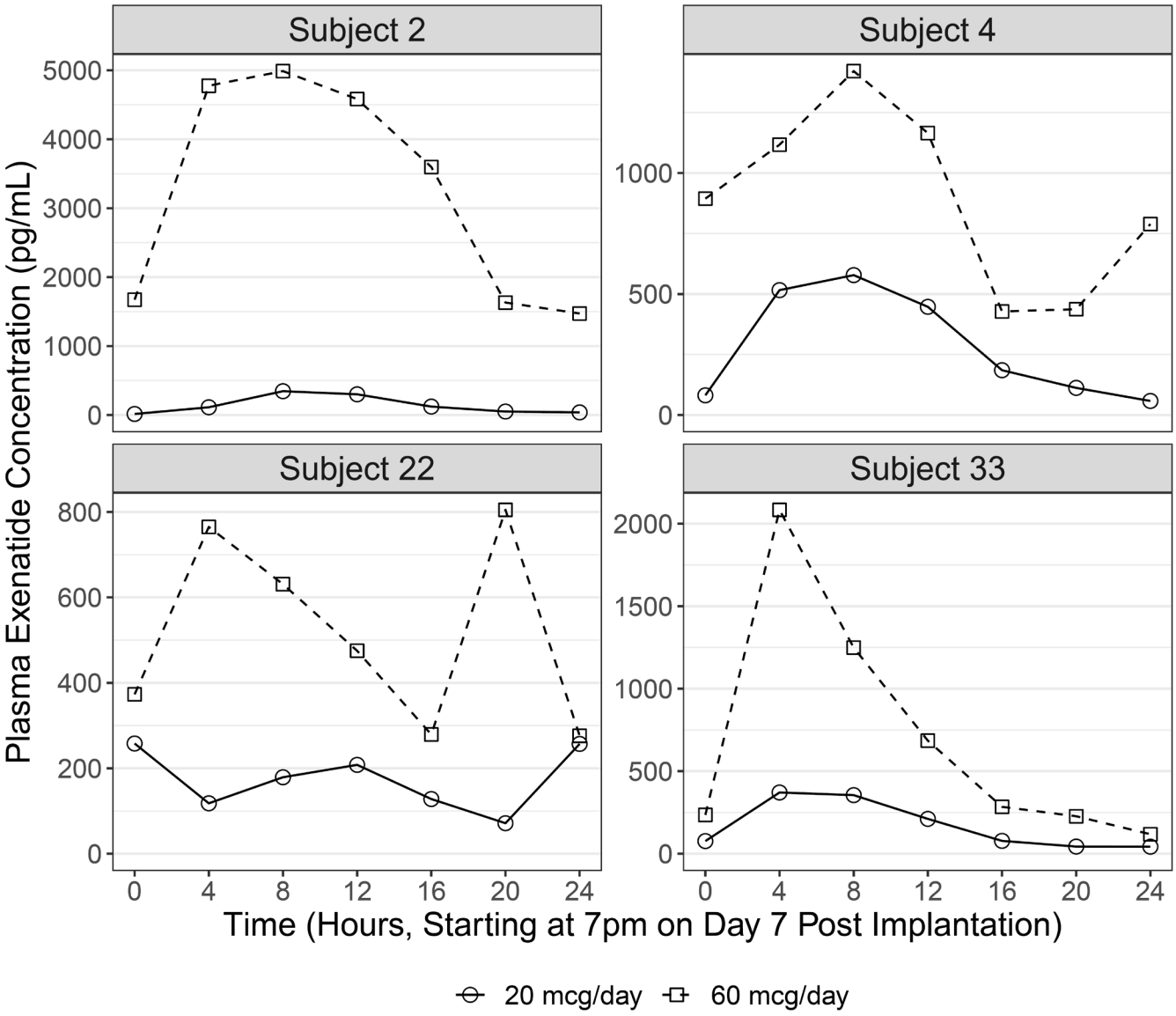
Figure 7. Variable Exenatide Exposures – Selected Subjects in Study CLP-116



Source: CDER Review staff. Analysis: R v. 4.2. using ADaM (adpc.xpt) from SDN0000.
Exenatide samples below the lower limit of quantification (LLOQ) are imputed as LLOQ/2
Four representative subjects are shown (n=27). Placebo data omitted. Refer to Section 5.3 for a presentation of all PK data from CLP-116
Pharmacokinetic sampling includes samples collected over a 24-hour period on Day 14 postimplantation.

Another Phase 1 study that provided frequent PK assessments was a study conducted to assess the effect of renal impairment on exenatide PK (Study CLP-109). All subjects received the same treatment (20 mcg ITCA 650 for 21 days, followed by 40 mcg ITCA 650 for 21 days, and followed by 60 mcg ITCA 650 for 9 to 11 days). This study also supports the observations from Study 116 and 103SS regarding the inconsistent release of exenatide in several subjects. Figure 8 shows plots from selected subjects who had large excursions with inconsistent release. The findings of such inconsistent release were observed in subjects regardless of renal function and antidrug antibody (ADA) status (see Figure 17 for all subjects' PK profiles).

Figure 8. Variable Exenatide Exposures – Selected Subjects in Study CLP-109



Source: CDER Review staff. Analysis: R v. 4.2. using ADaM (adpc.xpt) from SDN0000.
Exenatide samples below the lower limit of quantification (LLOQ) are imputed as LLOQ/2
Four representative subjects are shown (N=40). Refer to Section 5.3 for a presentation of all PK data from CLP-109.
Pharmacokinetic sampling included assessments for each treatment period (20 mcg device: preplacement, 4 and 8 hours postplacement, and Days 7-8; 60 mcg device; preplacement, 4 and 8 hours after placement, and Days 7-8, also 2, 4, 5, and 8 hours after removal of device (Day 9, 10, or 11).

Discussion of Pharmacokinetic Properties Specific to Injectable GLP1RAs

Shorter-acting GLP1RA products (e.g., Adlyxin and Byetta) exhibit rapid changes in drug concentrations in the sense that their respective active pharmaceutical ingredient is largely eliminated from the body between doses. The magnitude of the excursions, however, is limited by the dosing of the products: Byetta doses exenatide at a maximum of 10 mcg twice a day and Adlyxin doses lixisenatide at a maximum of 20 mcg daily. In contrast, IVR studies indicate that ITCA 650 may intermittently dispense at a rate of more than 100 mcg/day, as discussed in Section 3.1.

The approved long acting GLP-1RA exenatide containing product intended for weekly injection is Bydureon. Its PK is absorption limited (e.g., the absorption half-life of the product is much longer than the elimination half-life, also known as flip-flop kinetics). Thus, the absorption rate drives daily systemic exposure. The controlled absorption is a physical-chemical consequence of the formulation, thus limiting the potential for large rapid excursions in drug exposure. Bydureon is a microsphere formulation of exenatide; exenatide is loaded with a poly(lactic-co-glycolic acid) (PLGA) polymer that slowly degrades and releases the exenatide (Yu et al. 2018). A single injection of Bydureon releases predictably over 13 weeks, with the rate of release peaking around Week 7 (Fineman et al. 2011).

Other long-acting products have intrinsic properties that mitigate against marked excursions from steady-state exposures, including reliable dose accuracy of injection platforms (prefilled syringes, autoinjectors), and appropriate intervals of dose frequency relative to drug half-life and bioavailability. The total exposure to both exenatide in Bydureon (which has half-life controlled by absorption) and long-acting GLP1RAs (which has half-life controlled by elimination) at any given time is defined by the superposition of the PK profiles of each injection (i.e., up to 13 injections in patients using Bydureon as labeled).

Quantification of Variability and Rapid Excursions

Quantification and comparison of within-subject variability (WSV) in pharmacokinetics is challenging for a few reasons. First, clinical trials do not typically collect frequent pharmacokinetic samples, particularly in time periods relevant to detect rapid concentration excursions. Secondly, the estimate of variability is sensitive to the nature of the chosen time window (duration of window, time between samples). Lastly, even if ideal data were available, within-subject variability does not quantify infrequent but dramatic spikes, but rather average variability (e.g., the "spread" of the data over a specified sampling window). In other words, WSV reflects usual variability, but is insensitive to infrequent abrupt concentration increases.

Nonetheless, CDER reanalyzed the PK data from Study CLP-109 and CLP-103SS and estimated the WSV in individual exenatide concentrations collected over 24 hours (i.e., within-day WSV) as well as the between-day WSV in individual exenatide concentrations data collected across multiple days proximal to each other [i.e., within 72-hours of each other and compared to the WSV of Bydureon (from Studies 104 and 105)]. The results of the within-day WSV and between-day WSV are summarized below in Table 5.

Table 5. Comparison of Within-Subject Variability Between ITCA 650 and Bydureon

WSV	ITCA 650 (Study CLP-103SS)[a]	ITCA 650 (Study CLP-109)[b]	Bydureon (Study 104)[c]	Bydureon (Study 105)[c]
Within-day WSV	NA	66%	20%	21%
Between-day WSV	42%	68%	32%	30%

Source: CDER Review staff

[a] WSV was estimated as the residual error from an intercept-only linear mixed-effects model that was used to fit the log-transformed exenatide "steady-state" concentrations from a 60 mcg/day formulation. Between-subject variability was included on the intercept. The between-day WSV was comparable between Weeks 41, 52, and 65. The within-day variability cannot be estimated in the absence of within-day PK samples.

[b] WSV was estimated as the residual error from an intercept-only linear mixed-effects model that was used to fit the log-transformed dose-normalized exenatide "steady-state" concentrations from 20, 40 and 60 mcg/day formulations. Between-subject variability was included on the intercept.

[c] WSV for Bydureon was analyzed using an intercept-only linear mixed-effects model on log-transformed dose-normalized exenatide steady-state concentrations from 0.8 mg and 2 mg formulations from Studies CLP-104 and -105. Between-subject variability was included on the intercept.

Abbreviations: ITCA 650, exenatide in DUROS device; PD, pharmacodynamics; PK, pharmacokinetics; WSV, within-subject variability; NA, not applicable

These values reported in Table 5 for ITCA 650 are similar to the WSV of 65% (using individual concentrations over 24 hours in Study CLP-109) reported by the Applicant in their Summary of Clinical Pharmacology Studies. In

comparison, Bydureon showed a lower estimated within-day and between-day WSV of 20% and 30%, respectively.

Summary

The totality of available data that included more frequent sampling (multiple samples within 24 hours or on consecutive days) showed inconsistent exenatide release with marked excursions in some subjects and day-to-day variability for ITCA 650. These PK observations were consistent with the in vitro device performance for ITCA 650 regarding variable release exenatide using IVR, and with the manufacturing issues due to the nature of the drug (e.g., viscosity). PK was collected from 37 subjects randomized to a substudy of the glycemic control Study CLP-103, from a DDI Study CLP-116, and renal impairment Study CLP-109; where the sampling scheme allowed assessment of day-to-day variability in concentrations. These limited available data demonstrated that exenatide exposure fluctuated day-to-day in individual subjects with sudden increases in exenatide exposure observed, up to concentrations as high as >4000 pg/mL (whereas the half-maximal effective concentration of exenatide is approximately 150 pg/mL). CDER concluded that the available PK data are consistent with the CDRH device evaluation noting unreliable and inconsistent exenatide drug delivery and provide a potential link to the clinical safety findings in the drug development program discussed in Section 3.3.

3.3 Clinical Issues

Sources of Clinical Data for Efficacy and Safety

The Applicant conducted two Phase 3 studies to evaluate the safety and efficacy of ITCA 650: Study CLP-103, a placebo-controlled double-blind study that examined two dosing strategies, and Study CLP-105, an active-controlled double-blind study that compared the higher dosing strategy to sitagliptin. In addition, the Applicant conducted an event-driven CVOT (Study CLP-107 or FREEDOM) to evaluate noninferiority of ITCA 650 compared to placebo with regard to MACE, which is the source of most of the clinical safety data in the ITCA 650 clinical development program (Table 6).

Table 6. Clinical Studies Submitted to Establish Substantial Evidence of Safety and Effectiveness

Study	Trial Design	Regimen/Schedule/Route	Endpoints	Treatment Duration	N	Study Population	Number of Sites and Countries
CLP-103	Phase 3, multicenter, randomized, double-blind, **placebo-controlled, superiority trial**	**ITCA 650 subdermal:** 20 mcg/day for 13 weeks, then 40 or 60 mcg/day for 26 weeks **Comparator:** placebo for 39 weeks	A1C at 39 weeks: change from baseline (LOCF)	39 weeks	ITCA 650 20/40 mcg/day: **153** ITCA 650 20/60 mcg/day: **153** Placebo: **154** Total: **460**	Adults w/ T2DM ≥3 months; A1C ≥7.5% and ≤10% on stable regimen of diet, exercise ± Met/SU/TZD	126 sites, all in the United States
CLP-105	Phase 3, multicenter, randomized, double-blind, active control (sitagliptin), noninferiority trial	**ITCA 650 subdermal:** 20 mcg/day for 13 weeks, then 60 mcg/day for 39 weeks, plus matching placebo capsules **Comparator:** sitagliptin 100 mg orally daily, plus matching ITCA 650 subdermal placebo	A1C at 52 weeks: change from baseline (MMRM), NI margin 0.3%	52 weeks	ITCA 650 20/60 mcg/day: **268** Sitagliptin 100 mg/day: **267**	Adults w/ T2DM ≥3 months; A1C ≥7.5% and ≤10% on stable regimen of ≥1500 mg metformin daily	124 sites in 13 countries
CLP-107 (FREEDOM)	Phase 3, multicenter, randomized, double-blind, placebo-controlled, **CVOT**	**ITCA 650 subdermal:** 20 mcg/day for 13 weeks, then 60 mcg/day every 26 weeks **Comparator:** ITCA 650 subdermal placebo	Time to first occurrence of any 4-point MACE composite event (CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina)	**Event-driven** (treatment continued until 124 positively adjudicated 4-point MACE events were collected; **32 months**)	ITCA 650 20/60 mcg/day: **2075** ITCA 650 placebo: **2081**	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: Adapted from the Applicant's tabular listing of all clinical studies-resubmission and the respective CSRs for each trial submitted to NDA 209053, Seq. 0059.

Abbreviations: CSR, clinical study report; CVOT, cardiovascular outcomes trial; A1C, hemoglobin A1c; ITCA 650, exenatide in DUROS device; LOCF, last observation carried forward; MACE, major adverse cardiovascular event; Met, metformin; MMRM, mixed models repeated measures; NDA, new drug application; NI, noninferiority; SU, sulfonylurea; T2DM, type 2 diabetes mellitus; TZD, thiazolidinedione

Demographics, Baseline Characteristics

Table 7 and Table 8 display the baseline demographic and disease characteristics of randomized subjects in the Phase 3 clinical studies (demographics and baseline characteristics were balanced across treatment groups in each study). As is typical of Phase 3 glycemic control studies conducted to assess glycemic efficacy, subjects in CLP-103 and CLP-105 were not enriched for CV risk. By comparison, the subjects in CLP-107 (the CVOT) were enriched for CVD and so were older, had a longer history of diabetes, and a higher incidence of comorbidities.

Table 7. Demographics of ITCA 650 Phase 3 Clinical Studies (CLP-103, CLP-105, and CLP-107)

Parameter	CLP-103 N=460	CLP-105 N=535	CLP-107 (CVOT) N=4156
Male (%)	272 (59.1)	306 (57.2)	2631 (63.3)
Hispanic or Latino (%)	162 (35.2)	229 (42.8)	1161 (27.9)
Race (%)			
Asian	5 (1.1)	21 (3.9)	37 (0.9)
Black	64 (13.9)	62 (11.6)	186 (4.5)
Multiple	2 (0.4)	11 (2.1)	49 (1.2)
All other	9 (2.0)	29 (5.4)	62 (1.5)
White	380 (82.6)	412 (77.0)	3822 (92.0)
Age, years (median [IQR])	55 [48, 62]	56 [48, 61]	63 [57, 68]
Age group, years (%)			
<50	129 (28.0)	151 (28.2)	280 (6.7)
50-<65	256 (55.7)	297 (55.5)	2232 (53.7)
65-<75	68 (14.8)	74 (13.8)	1373 (33.0)
≥75	7 (1.5)	13 (2.4)	271 (6.5)

Source: Source: CDER Review staff. Analysis: R v. 4.2. using ADaM (adsl.xpt) from SDN0000.
ITT population.
Abbreviations: CVOT, cardiovascular outcomes trial; IQR, interquartile range; ITCA 650, exenatide in DUROS device; ITT, intent to treat

Table 8. Baseline Characteristics of ITCA 650 Phase 3 Clinical Studies (CLP-103, CLP-105, and CLP-107)

Parameter	CLP-103 N=460	CLP-105 N=535	CLP-107 N=4156
A1C, % (median [IQR])	8.4 [7.8, 9.1]	8.4 [7.8, 9.3]	8.0 [7.2, 9.3]
Antidiabetic drug use			
Metformin	392 (85.2)	530 (99.1)	3526 (84.8)
Sulfonylurea	217 (47.2)	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)
Systolic BP, mmHg (median [IQR])	132 [123, 142]	132.5 [123, 143]	137.5 [128, 147]
Diastolic BP, mmHg (median [IQR])	81 [76, 87.0]	80 [75, 87]	80 [73, 85]
Hypertensive	312 (67.8)	356 (66.5)	3616 (87.0)
Lipid abnormalities	299 (65.0)	294 (55.0)	2829 (68.1)
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)

Parameter	CLP-103 N=460	CLP-105 N=535	CLP-107 N=4156
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-I 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)
eGFR, mL/min/1.73m^2 (median [IQR])	85 [74, 99]	86 [75, 98]	80 [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)
>300 mcg/mg	NR	NR	280 (6.7)
≥30-≤300 mcg/mg	NR	NR	1139 (27.4)
BMI Category (%)			
<30 kg/m^2	143 (31.1)	224 (41.9)	1407 (33.9)
30-<35 kg/m^2	141 (30.7)	140 (26.2)	1400 (33.7)
≥35 kg/m^2	175 (38.0)	171 (32.0)	1337 (32.2)
Smoking history (%)			
Current smoker	61 (13.3)	84 (15.7)	651 (15.7)
Never smoked	298 (64.8)	337 (63.0)	2136 (51.4)
Past smoker	101 (22.0)	114 (21.3)	1368 (32.9)

Source: Source: CDER Review staff. Analysis: R v. 4.2. using ADaM (adsl.xpt) from SDN0000.
ITT population.
Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; CHF, coronary heart failure; CVA, cerebrovascular accident; eGFR, estimated glomerular filtration rate; IQR, interquartile range; ITCA 650, exenatide in DUROS device; ITT, intent-to-treat; MI, myocardial infarction; PAD, peripheral arterial disease; TZD, thiazolidinedione

Refer to Section 5.3 for the detailed inclusion criteria for Study CLP-107. In general, subjects in this study were required to be at least 40 years of age with documented coronary artery disease (CAD) or other ischemic vascular disease (cerebrovascular, peripheral arterial) (called the 'high-risk group'), or they were to be at least 60 years old with risk factors for these CV outcomes ('low-risk group').

Of the subjects randomized in CLP-107, 3159 of 4156 (76%) met the inclusion criteria for the high-risk CV group, whereas 997 of 4156 (24%) met the inclusion for the low-risk CV group. The ITCA 650 program included limited numbers of subjects with advanced CKD (Table 9); only one subject in CLP-103 had a baseline eGFR under 60 mL/min/1.73m^2, fewer than 5% of subjects in CLP-105 had a baseline eGFR under 60 mL/min/1.73m^2, and fewer than 10% of subjects in CLP-107 had a baseline eGFR under 60 mL/min/1.73m^2.

Overview of Glycemic Control Studies: Designs and Subject Disposition

Study CLP-103

Study CLP-103 was a multicenter, randomized, double-blind, placebo-controlled trial that randomized subjects in a 1:1:1 ratio to one of the following three treatment groups:

- Group 1: ITCA 650 20 mcg/day for 13 weeks, followed by ITCA 650 40 mcg/day[2] for 26 weeks
- Group 2: ITCA 650 20 mcg/day for 13 weeks, followed by ITCA 650 60 mcg/day for 26 weeks
- Group 3: ITCA 650 placebo (i.e., placebo devices) for total of 39 weeks (ITCA 650 placebo removed and replaced at Week 13)

Study CLP-103 evaluated the following endpoints using a serial gatekeeper strategy to maintain type I error. Alpha was split in half to compare the low and high dose to placebo:

1. Change from baseline in A1C at 39 weeks
2. Change in body weight
3. Proportion with A1C <7%

The demographic information for subjects in Study CLP-103 is shown in Table 7, and other baseline characteristics of the study population are shown in Table 8.

Study CLP-103 subject disposition is shown in Table 9; 19.6% of subjects in CLP-103 randomized to ITCA 650 60 mcg/day discontinued treatment before the primary efficacy endpoint. A similar rate of premature discontinuations was observed in the control arm, though the reasons for treatment discontinuation differed. The most common reason for treatment discontinuation from ITCA 650 was an AE. Review of the specific AE experienced at time of study treatment discontinuation showed more subjects discontinued ITCA 650 due to GI AEs (nausea, vomiting, diarrhea, abdominal pain, gastritis, dyspepsia, constipation) versus placebo: 11 discontinued from the ITCA 650 40 mcg/day arm, 11 from the ITCA 650 60 mcg/day arm, and 3 from the ITCA 650 placebo arm. 'Loss of glycemic control' and 'withdrawal by subject' were reasons for premature discontinuation more frequently reported by subjects randomized to placebo.

Table 9. Subject Disposition in Study CLP-103

Parameter	ITCA 650 40 mcg/day	ITCA 650 60 mcg/day	Placebo
Randomized (%)	153 (100.0)	153 (100.0)	154 (100.0)
Randomized and treated (%) (safety population)	153 (100.0)	153 (100.0)	154 (100.0)
Randomized and treated with a postbaseline A1C measurement (%) (mITT population)	147 (96.1)	151 (98.7)	143 (92.9)
Received glycemic rescue (%)	26 (17.0)	18 (11.8)	65 (42.2)

[2] The ITCA 650 40 mcg/day device was studied in CLP-103 but not proposed for marketing.

Parameter	ITCA 650 40 mcg/day	ITCA 650 60 mcg/day	Placebo
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)
AE	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.
Abbreviations: A1C, hemoglobin A1C; AE, adverse event; ITCA 650, exenatide in DUROS device; ITT, intent-to-treat; mITT, modified intent-to-treat

Study CLP-105

Study CLP-105 was a multicenter, randomized, double-blind (subjects randomized to ITCA 650 and placebo pill or to sitagliptin and placebo ITCA 650 device), active comparator trial that compared efficacy, safety, and tolerability of ITCA 650 to sitagliptin, both as add-on to metformin.

Study CLP-105 evaluated the following endpoints (at Week 52) using a serial gatekeeper strategy to maintain type I error:

1. Noninferiority, change in A1C
2. Superiority of A1C change
3. Superiority, A1C reduction >0.5% and weight loss ≥2 kg
4. Superiority, change in body weight
5. Superiority, proportion with A1C <7%

The demographic information for subjects in Study CLP-105 is shown in Table 7, and other baseline characteristics of the study population are shown in Table 8. Study CLP-105 subject disposition is shown in Table 10. Of the subjects assigned to ITCA 650, 23.9% stopped treatment prematurely compared with 18.7% of subjects assigned to sitagliptin. The imbalance in premature treatment discontinuations was primarily driven by more subjects withdrawing due to AEs from the ITCA 650 60 mcg/day study arm (31 of 268) than from the sitagliptin 100 mg/day study arm (10 of 267). Review of the AEs experienced at the time of premature treatment discontinuation showed that 25 of 268 in ITCA 650 60 mcg/day treatment group reported AEs consistent with GI intolerability compared to 3 of 267 in the sitagliptin 100 mg/day treatment group. Six of the ten patients in the sitagliptin plus placebo device group who discontinued due to AEs experienced AEs related to the ITCA 650 placebo device (e.g., hemorrhage at application site, application site pain, application site cellulitis).

Table 10. Subject Disposition in Study CLP-105

Parameter	ITCA 650 60 mcg/day	Sitagliptin 100 mg/day
Randomized (%)	268 (100.0)	267 (100.0)
Randomized and treated (%) (safety population)	265 (98.9)	265 (99.3%)
Randomized and treated with a postbaseline A1C measurement (%) (mITT population)	263 (98.1)	257 (96.)
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)
AE	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)
Pregnancy	0 (0.0)	1 (0.4)
Excluded medication	0 (0.0)	1 (0.4)
Withdrawal by subject	18 (6.7)	21 (7.9)
Completed follow-up visit (%)	248 (92.5)	247 (92.5)

Source: Source: CDER Review staff. Analysis: R v. 4.2 using ADaM (adsl.xpt) from SDN0000.
ITT population.
Abbreviations: AE, adverse event; Hb1Ac, hemoglobin 1Ac; ITCA 650, exenatide in DUROS device; ITT, intent-to-treat; mITT, modified intent-to-treat

Study CLP-107 (FREEDOM) CVOT

Study CLP-107 was a randomized, multicenter study to evaluate CV outcomes with ITCA 650 in subjects treated with standard of care for T2DM. Subjects were randomized to the proposed to-be-marketed dosing regimen of ITCA 650 (initial implant of a 20 mcg/day device followed by a 60 mcg/day device replaced every 26 weeks) versus a ITCA 650 placebo device (same device but without exenatide).

Subject disposition for Study CLP-107 is shown in Table 11. Similar to the observations from CLP-103 and CLP-105, the majority of treatment discontinuations in subjects assigned to ITCA 650 were due to AEs. Of the 2070 subjects who received ITCA 650, 258 (12.4%) discontinued due to AEs: 84 (4.1%) discontinued due to nausea, 42 (2%) discontinued due to vomiting, and 10 (0.3%) discontinued due to diarrhea. In addition, treatment discontinuations due to various device complications occurred in subjects given active treatment as well as those given ITCA 650 placebo. Figure 9 shows the treatment discontinuations and treatment discontinuations due to AEs over time. The data show that AEs leading to treatment discontinuations were somewhat more frequent around the time of device removal/replacement but could occur at any time.

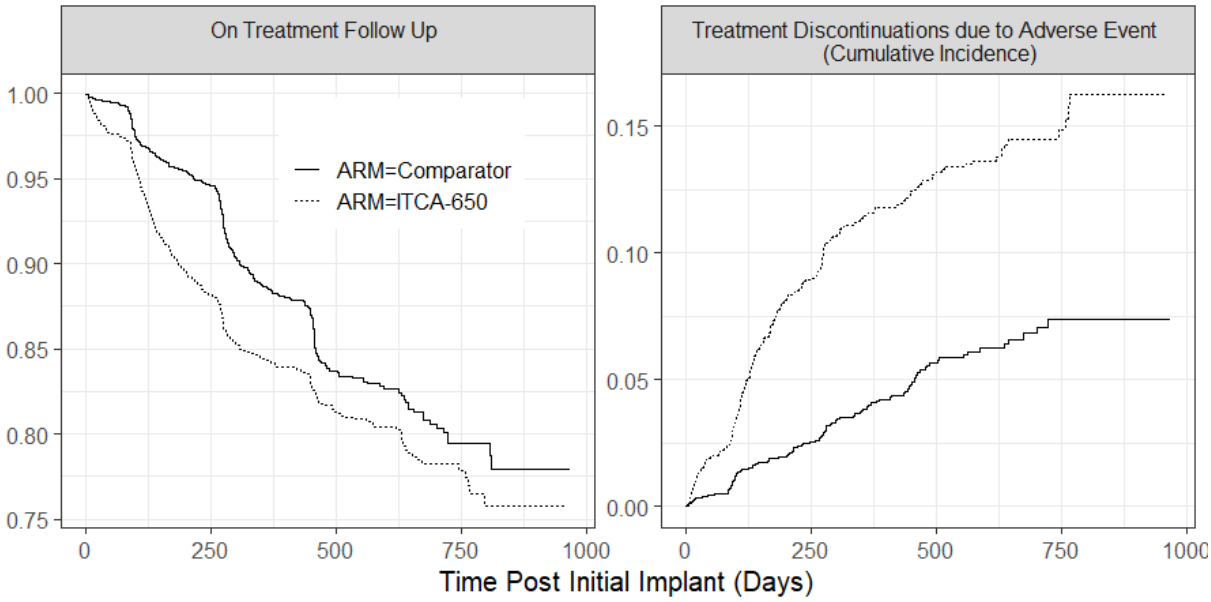
Table 11. Subject Disposition in Study CLP-107

Parameter	ITCA 650 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)

Parameter	ITCA 650 60 mcg/day	PLACEBO
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)
Loss of glycemic control	0 (0.0)	8 (0.4)
Loss to follow-up	7 (0.3)	6 (0.3)
Excluded medication	2 (0.1)	12 (0.6)
Other	35 (1.7)	41 (2.0)
Withdrawal by subject	68 (3.3)	124 (6.0)
Completed study (%)	1996 (96.2)	2007 (96.4)
Discontinued study (%)	79 (3.8)	74 (3.6)
AE	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)

Source: CDER Review staff. Analysis: R v. 4.2 using ADaM (adsl.xpt) from SDN0000.
ITT population.
Abbreviations: AE, adverse event; ITCA 650, exenatide in DUROS device; ITT, intent-to-treat

Figure 9. On-Treatment Follow-Up and Treatment Discontinuations Due to AEs for CLP-107



Source: CDER Review staff. Analysis: R v. 4.2 (Disposition); data: adsl.xpt from SDN0000.
Censoring time defined as the difference in days between initial procedure date and treatment removal date, plus 1 day.
Events were defined as all-cause premature treatment discontinuation (left panel) and premature treatment discontinuation due to AE (right panel).
Right panel: treats administrative censoring, loss of glycemic control, loss to follow-up, pregnancy, withdrawal by subject, or other the same.
Abbreviations: AE, adverse event; ITCA 650, exenatide in DUROS device

3.3.1 Efficacy Summary

Table 12 (Study CLP-103) and Table 13 (Study CLP-105) summarize the statistical methods and primary efficacy results based on the Applicant's analyses and the CDER reviewer's analyses. In particular, the CDER reviewer's analyses were post hoc in an attempt to address the major efficacy review issues identified in the original NDA submission. Section 5.4 elaborates the details of these efficacy review issues and CDER's efforts to address them to evaluate the efficacy of ITCA 650. Despite the difference in the statistical approaches, both the Applicant's

and the CDER reviewer's analyses demonstrated statistically significant treatment effects with respect to A1C reduction from baseline for both Studies CLP-103 and CLP-105. The estimated treatment effects based on the CDER reviewer's analyses are of smaller magnitude and have larger variability than the results from the Applicant's analyses. The analyses from the CDER reviewer support the conclusion that ITCA 650 is efficacious when compared to either placebo or sitagliptin. However, due to a high missing data rate and mismatched visit windows, determining a reliable estimate for the real treatment effect remains a challenge.

Table 12. Primary Efficacy Analyses on A1C Change From Baseline at Week 39, Study CLP-103

Population	Method	Statistic	ITCA 650 40 mcg/day	ITCA 650 60 mcg/day	Placebo
Applicant's analysis					
Applicant defined mITT population, excluding subjects who did not return for their first study visits	ANCOVA LOCF Excluding observations after rescue	N	147	151	143
		Baseline, mean (SD)	8.5 (0.8)	8.4 (0.8)	8.5 (0.8)
		LS Mean (SE)	-1.0 (0.1)	-1.1 (0.1)	-0.1 (0.1)
		LS Difference (97.5% CI)	-1.0 (-1.3, -0.7)	-1.1 (-1.4, -0.8)	
		p-Value (two-sided)	<0.001	<0.001	
CDER Reviewer's analysis					
All randomized subjects who received treatment	ANCOVA with MI based on baseline washout Using ±25-day visit window	N	153	153	154
		Baseline, mean (SD)	8.5 (0.8)	8.4 (0.8)	8.5 (0.8)
		LS Mean (SE)	-1.0 (0.1)	-1.1 (0.1)	-0.3 (0.1)
		LS Difference (97.5% CI)	-0.7 (-1.0, -0.4)	-0.7 (-1.0, -0.4)	
		p-Value (two-sided)	<0.001	<0.001	

Source: Clinical Study Report for CLP-103, and CDER review staff. Analysis: SAS v. 9.4; datasets: adsl.xpt and adlb.xpt from SDN0000.
Abbreviations: ANCOVA, analysis of covariance; CDER, Center for Drug Evaluation and Research; ITCA 650, exenatide in DUROS device; LOCF, last observation carried forward; LS, least squares; MI, multiple imputation; mITT, modified intent-to-treat; N, number of subjects; SD, standard deviation; SE, standard error

Table 13. Primary Efficacy Analyses on A1C Change From Baseline at Week 52, Study CLP-105

Population	Method	Statistic	ITCA 650 60 mcg/day	Sitagliptin 100 mg/day
Applicant's analysis				
Applicant defined mITT population, excluding subjects who did not return for their first study visits	MMRM Excluding observations after rescue	N	263	257
		Baseline, mean (SD)	8.5 (0.9)	8.7 (0.9)
		LS Mean (SE)	-1.5 (0.1)	-0.8 (0.1)
		LS Difference (95% CI)	-0.7 (-0.9, -0.5)	
		p-Value (two-sided)	<0.001	
CDER Reviewer's analysis				
All randomized subjects who received treatment	ANCOVA with MI based on baseline washout using ±25-day visit window	N	265	265
		Baseline, mean (SD)	8.5 (0.9)	8.7 (0.9)
		LS Mean (SE)	-1.3 (0.1)	-0.9 (0.1)
		LS Difference (95% CI)	-0.4 (-0.6, -0.2)	
		p-Value (two-sided)	<0.001	

Source: Clinical Study Report for CLP-105, and CDER review staff. Analysis: SAS v. 9.4; datasets: adsl.xpt and adlb.xpt from SDN0000 and SDN0006.
Abbreviations: A1C, hemoglobin A1C; ANCOVA, analysis of covariance; CDER, Center for Drug Evaluation and Research; CI, confidence interval; ITCA 650, exenatide in DUROS device; LOCF, last observation carried forward; LS, least squares; MI, multiple imputation; mITT, modified intent-to-treat; MMRM, mixed models for repeated measures; N, number of subjects; SD, standard deviation; SE, standard error

For both Study CLP-103 and CLP-105, the CDER reviewer and the Applicant also analyzed the secondary endpoint of weight loss, with similar analysis methods as applied in the primary analyses. Specifically, visits within a ±25-day window were used for the CDER reviewer's analysis. Based on the CDER reviewer's analyses, the results for the difference of weight loss at Week 39 compared to placebo (97.5% confidence interval [CI]) were -1.6 kg (-2.8, -0.4) for ITCA 650 40 mcg/day and -2.2 kg (-3.4, -1.0) for ITCA 650 60 mcg/day in Study CLP-103. In Study CLP-105, the difference of weight loss at Week 52 compared to sitagliptin 100 mg/day was –1.8 kg (95% CI: -2.8, -0.8) for ITCA 650 60 mcg/day.

3.3.2 Safety Issues

3.3.2.1 GI AEs

Adverse events of nausea, vomiting, and diarrhea were common in subjects randomized to ITCA 650 across the core clinical trials. Due to limitations of pooling disparate studies, and the fact that FREEDOM contributed most of the GI AEs, CDER presents only the results from FREEDOM. As discussed in Section 3.3, treatment discontinuations due to events of nausea, vomiting, and diarrhea (among other AEs leading to treatment discontinuation) were observed in the clinical trials.

Typical AE analysis methods measure incidence (i.e., number of patients reporting at least one AE, or time to first event), rather than counting all occurrences (i.e., frequency of event). Frequency of events may also be relevant since individual patients—especially those most susceptible—may have recurrent events (but are counted only once for incidence). Therefore, CDER assessed cumulative number of events as well as incident events of nausea, vomiting, diarrhea. Figure 10 shows that there are increases in GI events (including all events, not just the incident event) related to the initiation of treatment (with the 20 mcg/day device) and titration (transition to the 60 mcg/day device). In addition, there are increases in events related to subsequent device removal and insertion procedures (the "staircase" pattern with 6-month intervals), as well as accumulation of events beyond periods of recent device changes. Finally, CDER identified only three SAEs of nausea, vomiting, and diarrhea among subjects who received ITCA 650, versus none among subjects who received placebo; however, review of narratives for other SAEs identified cases in which GI symptoms were reported in the

context of these other events but not coded as GI SAEs in the datasets. Taken together, this suggests that the risk of nausea and vomiting is not restricted to the period of treatment initiation.

Table 14. Treatment-Emergent AEs of Nausea and Vomiting, and Diarrhea (On-Treatment Narrow FMQ*) in FREEDOM

	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
All nausea	564 (25)	86 (3)	22.0	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

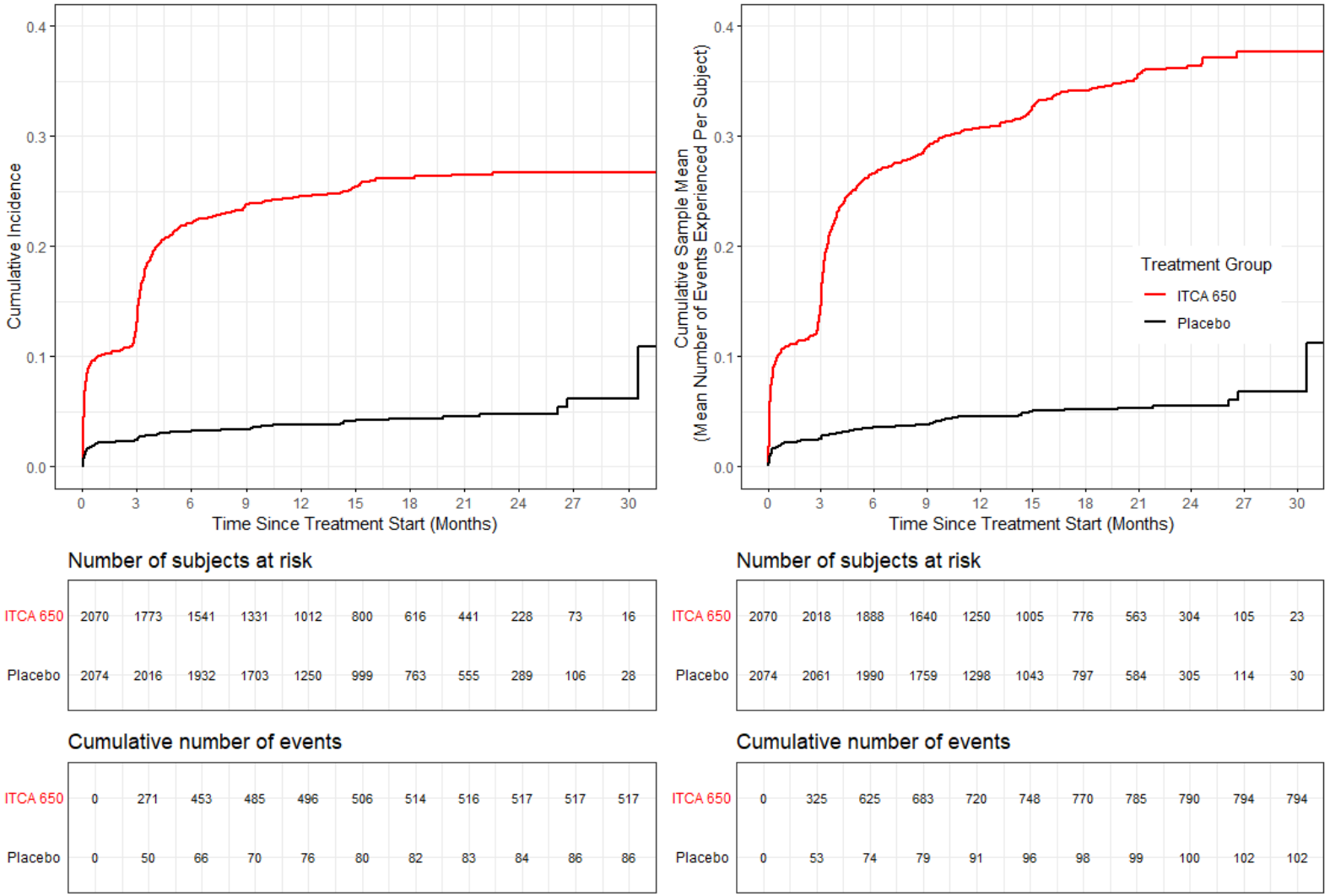
Source: CDER Review staff. Analysis: R v. 4.3; data: adae.xpt and adsl.xpt from SDN0000.

* FDA MedDRA Query (FMQ) Version 2.1. FDA has developed MedDRA queries (FMQs) based on grouping related PTs to search the clinical safety database for safety signals (see also Section 3.3.2.2 and Appendix 5.2 for a complete list of PTs in these queries).

Investigator attribution of intensity.

Abbreviations: AE, adverse event; FMQ, FDA Medical Query; ITCA 650, exenatide in DUROS device; MedDRA, Medical Dictionary for Regulatory Activities; PT, preferred term; PY, person-years

Figure 10. Cumulative Incidence (Time to First Event) and Cumulative Sample Mean (All Events) for Nausea and Vomiting (On-Treatment Narrow FMQ)



Source: CDER Review staff. Analysis: R v. 4.3, survival package (Therneau and Grambsch 2000; Therneau 2023). Data: adae.xpt and adsl.xpt from SDN0000.
Only treatment-emergent AEs occurring within 30 days of device removal are counted), mITT population.
The left panel displays time to first event estimates using the Kaplan-Meier estimator. The right panel displays a recurrent time to event model using a Nelson-Aalen Estimator. This latter analysis treats recurrent events and first events the same.
Abbreviations: AE, adverse event; FMQ, FDA Medical Query; ITCA 650, exenatide in DUROS device; mITT, modified intent-to-treat

3.3.2.2 AKI

In the ITCA 650 clinical development program there was an imbalance in overall and serious AKI events unfavorable to ITCA 650. Because of the observed AKI imbalance as reported by the Applicant, CDER conducted several additional analyses of AKI in the ITCA clinical studies, described in detail in this section.

Ascertainment Methods

The Applicant evaluated AKI as an AE of special interest based upon standard spontaneous AE reporting. The trial did not include additional specific ascertainment methods (e.g., a dedicated case report form). The Medical Dictionary for Regulatory Activities (MedDRA) and FDA have developed "broad" and "narrow" standardized MedDRA queries (SMQs) and FDA MedDRA queries (FMQs) based on grouping related preferred terms to search the clinical safety database for safety signals. The Applicant queried spontaneously reported AEs using the SMQ of acute renal failure (ARF) (narrow scope – see Table 29 for a complete list of Preferred Terms included in this SMQ). Clinical narratives are available only for AEs that were classified as SAEs or that resulted in death; therefore, narratives are not available for AKI events coded as nonserious.

CDER first analyzed the AKI events in the core clinical trials (CLP-103, CLP-105, and CLP-107/FREEDOM) using the Applicant's specified search strategy (i.e., MedDRA query SMQ ARF [narrow]). The Applicant restricted its analysis of AKI to events that occur or worsen "On-Treatment" (i.e., the Applicant did not include in its analysis AKI events that occurred before the device was implanted or that occurred more than 30 days after the device was removed). CDER corroborated the "On-Treatment" analysis and also conducted an alternate analysis using an "On-Study" censoring scheme (which includes AKI events that occur or worsen at any time after first exposure to the investigational agent until the end of the study).

CDER applied both the "On-Treatment" and "On-Study" censoring strategies because they have complementary strengths and weaknesses. "On-Treatment" safety analyses are conducted in subjects remaining on study drug, hence are no longer in the intact randomized treatment groups (i.e., groups balanced by randomization). Because this analysis focuses only on AEs while subjects are actually on drug (i.e., omits AEs that occur once patients are off of study drug), it may be more temporally sensitive to direct adverse responses to the drug. However, this approach may be affected by post-randomization confounding and may either over or underestimate an actual risk. "On-Study" safety analyses maintain randomization but include events in subjects no longer on study drug (and could still reflect toxicity of the drug). This approach may underestimate an actual risk that ameliorates soon after treatment discontinuations. "On-Treatment" and "On-Study" censoring schemes are also discussed in the section on MACE safety analyses (Section 3.3.2.3).

AKI Analysis Results

Based on the same standardized MedDRA query (v. 18.1) specified by the Applicant (ARF, narrow), in the core clinical trials (CLP-103, CLP-105, and CLP-107), CDER identified 46 of the 2488 subjects (1.8%)[3] randomized to the ITCA 650 20/60 mcg treatment arms who experienced AKI events (serious and nonserious) versus 25 of the 2493 subjects (1.0%) randomized to the placebo or active comparator treatment arms. The query identified a total of 79 AKI events in these 71 subjects: 52 events occurred in the ITCA 650 treatment arm compared to 27

[3] The calculation does not include the 153 subjects in CLP-103 who received treatment with the ITCA 650 40 mcg/day device, as the ITCA 650 40 mcg/day treatment arm studied a different dosing strategy using a different product not proposed for marketing. In addition, inclusion of the treatment arm introduces the potential for confounding due to Simpson's Paradox. However, if one includes those subjects, the rate of all AKI is 1.7% and the rate of serious AKI is 0.53% among subjects who received ITCA 650.

events in the comparator arms. Serious AKI AEs were reported in 14 subjects (0.56%) who received ITCA 650 versus 4 subjects (0.16%) who received placebo.

As discussed below and detailed in Table 16, review of the death narratives for all subjects in CLP-103, CLP-105, and CLP-107 classified as having experienced a nonserious AKI event identified two subjects who had received ITCA 650 and died during an AKI event: CDER confirmed that no deaths occurred among subjects randomized to placebo or active comparator in CLP-103, CLP-105, and CLP-107 who experienced an AKI event coded as nonserious. One subject experienced recurrent hospitalization for vomiting, AKI, and chest pain starting 4 days after his fourth removal/replacement procedure. His admitting diagnosis for the first hospitalization was chest pain and AKI, his discharge diagnosis was atypical chest pain due to vomiting. He was readmitted approximately 3 months later with chest pain and AKI and treated with dialysis; this subject ultimately died of multiorgan failure, and this case was not reported as a SAE of AKI. The second subject presented to clinic 19 days after his first ITCA 650 60 mcg/day device placement complaining of poor appetite, fatigue, hypoglycemia and requesting "review of their chemistry and lipase be drawn". The subject's serum creatinine had increased from a baseline of 1.3 mg/dL to 1.6 mg/dL and the eGFR had decreased from a baseline of 55 mL/min/1.73m^2 to 43 mL/min/1.73m^2. He was advised to stop metformin and maintain hydration. The subject was found dead at home 8 days later. Neither of these two events was coded as a serious AKI event. CDER therefore considers the imbalance in serious AKI events to be up to 16 subjects (0.64%) versus 4 subjects (0.16%). However, CDER did not include these additional events in the analyses presented in Table 15, which are based on the Applicant's event ascertainment.

All but one serious AKI event and all but 4 nonserious AKI events occurred in Study CLP-107 (FREEDOM CVOT), the largest study with the longest median follow up time. Baseline eGFR is associated with risk of AKI events (Grams et al. 2010); e.g., patients with eGFR below 60 mL/min/1.73m^2 have greater risk than patients with higher eGFR. Only a limited number of subjects with chronic kidney disease (CKD) stage 3 or worse were enrolled in any of the trials, including FREEDOM: as previously noted, only one subject in CLP-103 had a baseline eGFR under 60 mL/min/1.73m^2, fewer than 5% of subjects in CLP-105 had a baseline eGFR under 60 mL/min/1.73m^2, and fewer than 10% of subjects in CLP-107 had a baseline eGFR under 60 mL/min/1.73m^2 at baseline. The AKI signal in FREEDOM was observed in a population less susceptible to AKI, whereas no AKI signal was observed in the other GLP1RA CVOTs which studied populations more susceptible to AKI (see Table 21) – further indicating that the risk of AKI associated with use of ITCA 650 is greater than the risk of AKI associated with currently marketed GLP1RAs.

Table 15 summarizes pertinent clinical information for subjects who experienced AKI SAEs in either treatment arm of CLP-103, CLP-105, and CLP-107. One subject in each treatment arm required dialysis. In the ITCA 650 treatment arm 13 of 14 subjects recovered from the event. Seven (7) of the 14 AKI SAEs identified in subjects randomized to ITCA 650 occurred while subjects had the initial ITCA 650 20 mcg/day device in place (i.e., prior to up-titration to the ITCA 650 60 mcg/day device). Events occurred as long as 109 days after the most recent device replacement procedure. Inspection of the clinical narratives of AKI SAE cases that occurred among subjects receiving ITCA 650 showed that the unfavorable imbalance may have been caused by ITCA 650 treatment because GLP1RA products have a well-established causal relationship with GI adverse reactions (e.g., nausea, vomiting, and diarrhea) and 11 of 14 subjects in the ITCA 650 treatment arm who had AKI SAEs experienced GI AEs preceding the SAE (Table 15, see Section 5.1 for synopses of additional narrative details).

Baseline eGFR category was coded as mild renal impairment (baseline eGFR 60 to 89 mL/min/1.73m^2) for 9 subjects and moderate renal impairment (baseline eGFR 30 to 59 mL/min/1.73m^2) for 5 subjects who had AKI SAEs in the ITCA 650 treatment arm. As shown in Table 30 (Section 5.2) among these 5 subjects categorized as

moderately renally impaired at baseline, two subjects had baseline eGFRs of 57 and 58 mL/min/1.73m^2, respectively, and no subject had baseline eGFR <45 mL/min/1.73m^2. In addition, as noted in Table 16, one subject who died during an AKI coded as nonserious had a baseline eGFR of 88 mL/min/1.73m^2 and the other had a baseline eGFR of 55 mL/min/1.73m^2.

Table 15. Analysis of Subjects in CLP-103, CLP-105, and CLP-107 with SAEs of AKI

Parameter	ITCA 650 N=2488	Comparator N=2493
N (%)	14 (0.56)	4 (0.16)
Outcome of AE, N (%)		
Not recovered/resolved	0 (0.0)	1 (25.0)
Recovered/resolved	13 (92.9)	3 (75.0)
Required dialysis	1 (7.1)	1 (25.0)
Recovered/resolved w/sequelae	1 (7.1)	0 (0.0)
Related to permanent treatment discontinuation, N (%)	3 (21.4)	0 (0.0)
Days since last treatment procedure		
Median [IQR]	24 [6, 46]	46 [11, 104]
Minimum, maximum	0, 109	0, 185
Days since randomization		
Median [IQR]	93 [11, 301]	314 [153, 503]
Minimum, maximum	1, 748	107, 632
Last device in place at time of AE		
0 mcg/day	0 (0)	4 (100)
20 mcg/day	7 (50)	0 (0.0)
60 mcg/day	7 (50)	0 (0.0)
Duration of hospital stay (median [IQR])	4 [3, 5]	8 [6, 10]
GI AEs reported preceding AE	11 (78%)	3 (75%)

Source: CDER Review staff; analysis: R v. 4.2 adae.xpt SDN0000 (AKI_tables_18.1.R).

Abbreviations: AE, adverse event; AKI, acute kidney injury; GI, gastrointestinal; IQR, interquartile range; ITCA 650, exenatide in DUROS device; SAE, serious adverse event

Table 16. Summary of Deaths Preceded by AKI Events Coded as Nonserious

Case Number	Dosing Regimen	Study Day	GI Symptoms Preceding AKI	Synopsis
Uncoded Serious AKI Event 1	ITCA 650 60 mcg	649 (11 days after device replacement, recurring at 119 days after device replacement)	Yes	70 yo M w/ baseline Cr 0.9 (eGFR 88 mL/min/1.73m^2) who was noted to have increased Cr to 1.4 on the day of the fourth device replacement (Study Day 638). On Study Day 642, 4 days after fourth device replacement the subject was diagnosed with "viral gastroenteritis" with symptoms of dehydration, malaise, vomiting and diarrhea. On Study Day 649, he was admitted to a hospital with chest pain and acute kidney injury. He was discharged from the hospital on Study Day 652 with a diagnosis of atypical chest pain due to vomiting; concomitant ACEI and furosemide were stopped. Serum creatinine and BUN lab values are not available during or after this hospitalization, but AKI and gastroenteritis were reported as resolved by Study Day 654 and ACEI and furosemide were restarted on Study Day 655. On Study Day 757, he presented to a hospital again with chest pain and was admitted with a diagnosis of NSTEMI and acute renal failure. The subject was placed on heparin and IV fluid resuscitation, but renal function continued to decline, progressing from oliguria to anuria. The subject was transferred to another hospital. On arrival, the subject experienced nausea and hematemesis and was admitted with a diagnosis of acute renal failure (Cr 4.4) complicated by GI bleeding and pulmonary edema. The subject was treated with dialysis and ultimately died; the cause of death was coded as "multiorgan failure".
Uncoded Serious AKI Event 2	ITCA 650 60 mcg	110 (19 days after device replacement)	Yes	67 yo M w/ baseline Cr 1.3 (eGFR 55 mL/min/1.73m^2), who presented 19 days after placement of the first ITCA 650 60 mcg device w/ poor appetite, fatigue, and hypoglycemia, found to have AKI (Cr 1.6). Instructed to stop metformin and maintain hydration. Found dead at home 8 days later.

Source: CDER Review staff; summarized from Study CLP-107 Clinical Study Report (SDN0000).
Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AKI, acute kidney injury; Cr, creatine; CV, cardiovascular; GI, gastrointestinal; ITCA 650, exenatide in DUROS device; M, male; MACE, major adverse cardiovascular event; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction

AKI Events in FREEDOM

Because 74 of the 79 total AKI events identified by the Applicant were observed in CLP-107, as well as demographic differences between CLP-103 and CLP-105 with CLP-107 (Table 7), and differences in study design, CDER considers that the data in FREEDOM were most suitable to further assess AKI risk. CDER notes that the distribution of the 5 AKI events observed in CLP-103 and CLP-105 comprised 4 events (including 1 SAE) among subjects randomized to ITCA 650, one nonserious event in a subject randomized to sitagliptin, and no events among subjects randomized to ITCA placebo.

CDER presents analyses based on events identified using the Applicant's specified AKI query (i.e., ARF SMQ Narrow) in Table 17, as well as alternative search strategies: FDA interrogated the AE database of FREEDOM

with several different approaches (serious versus nonserious AKI events, FMQ versus SMQ[4] search strategies, broad versus narrow preferred term groupings); CDER analyzed the AKI events identified using both On-Treatment and On-Study censoring. A comprehensive table of both On-Treatment and On-Study of AKI events identified using all search strategies and all censoring schemes are listed in Table 17. Regardless of the search strategy and censoring scheme applied, the imbalance in AKI events unfavorable to ITCA 650 in the FREEDOM trial is apparent.

[4] See the Appendix for details on the preferred terms used in the broad and narrow FDA and MedDRA queries.

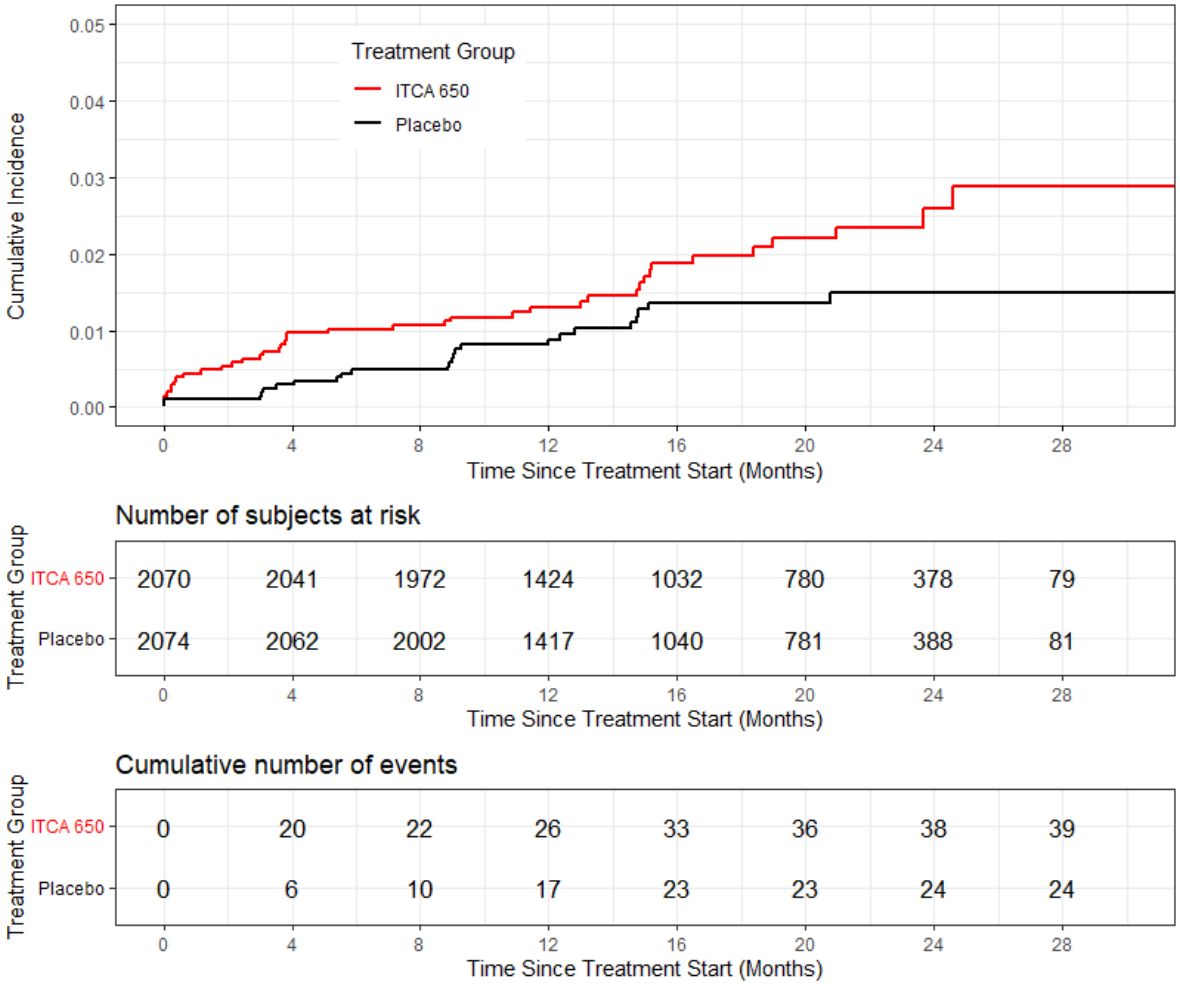
Table 17. Incidence of Treatment-Emergent AKI in Study CLP-107 Using Multiple Query Methodologies (mITT Population)

Parameter			Ascertainment Window	ITCA 650 (n=2070) N (%) [Events] [[IR]]	Placebo (n=2074) N (%) [Events] IR	HR (95% CI)	Incidence Rate Difference Incidence/100 PY (95% CI)
Serious and Nonserious	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)	0.5 (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)
Serious Only	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)

Source: CDER Review staff. Analysis: R v. 4.2 (AKI_tables_18.1.R); data: adae.xpt and adsl.xpt from SDN0000.
MedDRA v. 18.1, FMQ v. 2.1.
Modified intent-to-treat analysis includes subjects who were randomized and had at least one device placed.
Treatment-emergent defined as AEs that emerge or worsen after the start of treatment (September 1998).
Abbreviations: AKI, acute kidney injury; CI, confidence interval; FMQ, FDA medical query; HR, hazard ratio; IR, incidence rate (per 100 PY of follow-up); ITCA 650, exenatide in DUROS device; MedDRA, Medical Dictionary for Regulatory Activities; mITT, modified intent-to-treat; N, number of subjects experiencing at least one AE; OT, On-Treatment; OS, On-Study; PY, patient-years of follow-up; SMQ, standardized Medical Dictionary for Regulatory Activities query

Figure 11 shows CDER's time-to-first-event analysis of nonserious and serious AKI events in the FREEDOM study. Early separation of the curves is observed, with excess AKI events in the ITCA 650 treatment arm accruing throughout the study.

Figure 11. Kaplan-Meier Plot for Serious and Nonserious AKI (SMQ Acute Renal Failure – Narrow)* in CLP-107 (FREEDOM)



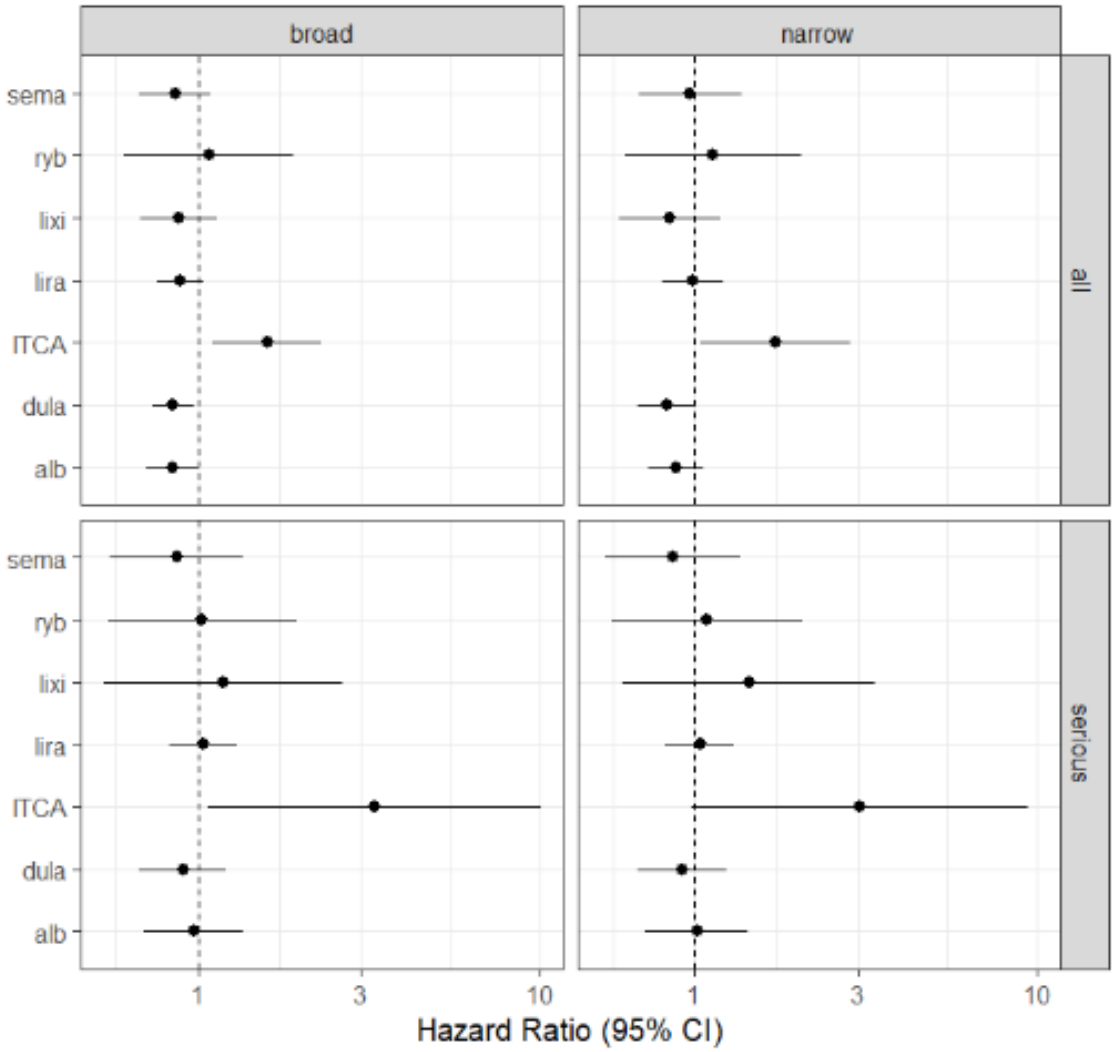
Source: CDER Review staff. Analysis: R v. 4.2 (AKI_tables_18.1.R); data: adae.xpt and adsl.xpt from SDN0000.
* Specified AESI.
MedDRA v. 18.1.
Modified intent to-treat analysis includes subjects who were randomized and had at least one device placed.
Abbreviations: AESI, adverse event of special interest; AKI, acute kidney injury; ITCA 650, exenatide in DUROS device; MedDRA, Medical Dictionary for Regulatory Activities; SMQ, standardized Medical Dictionary for Regulatory Activities query

Given the known safety profile of GLP1RAs and the association of GI AEs with dehydration that could precipitate AKI, CDER also conducted detailed analyses examining GI AEs (Section 3.3.2.1). As expected, an increase in GI AEs associated with ITCA 650 was observed. This finding is anticipated given that the clinical development programs for all GLP1RA products demonstrated a relationship between the products and nausea, vomiting, and diarrhea. However, an imbalance in serious AKI events is unique to FREEDOM among the CVOTs in the class: CDER's review of the narratives of serious AKI events that occurred in the ITCA 650 treatment arms revealed 11 of 14 events described GI symptoms (e.g., nausea and vomiting) and dehydration that preceded development of AKI. Finally, as detailed previously in the summaries of patient dispositions for CLP-103, CLP-105, and CLP-107, AEs of nausea, vomiting, and diarrhea resulting in treatment discontinuation were also common (Section 3.3.2). The next section provides information on AKI events in CVOTs from other GLP1RA agents.

AKI Reported in CVOTs in the GLP1RA Drug Class

CDER interrogated the CVOTs of the approved GLP1RA products with the same censoring schemes, SMQs, and FMQs as were applied to FREEDOM. Results of the ARF SMQ Narrow (the Applicant's specified query) and ARF SMQ Broad for FREEDOM are shown in Figure 12, using the On-Study censoring scheme, along with the same analysis for the other GLP1RA CVOTs; results from all other queries applied yielded consistent results (not shown). CDER notes that the imbalance in AKI seen in FREEDOM (labeled ITCA in Figure 12) was not observed in other CVOTs in the GLP1RA class. This imbalance in AKI was observed despite FREEDOM enrolling a lower proportion of subjects with baseline moderate-to-severe renal impairment compared with other CVOTs in the GLP1RA drug class, such that the FREEDOM population would be expected to have lower baseline risk for AKI events (Table 21).

Figure 12. Hazard Ratios for Time to First Occurrence of AKI (ARF SMQ Broad and Narrow) for All Marketed GLP1RA CVOTs*



Source: CDER Review staff; software: R v. 4.2; script: SAE analysis R; data: curated from NDA 209053 (adsl.xpt and adae.xpt, SDN0000) and confidential commercial information from other NDA/BLAs.

* 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.

Abbreviations: AKI, acute kidney injury; alb, albiglutide (HARMONY); ARF, acute renal failure; CI, confidence interval; CVOT, cardiovascular outcomes trial; dula, dulaglutide (REWIND); GLP1RA, glucagon-like peptide-1 receptor agonist; ITCA, exenatide (FREEDOM); lixi, lixisenatide (ELIXA); ryb, oral semaglutide (PIONEER-6); Sema, semaglutide (SUSTAIN-6); SMQ, standardized Medical Dictionary for Regulatory Activities query

Of note, the labeling for all marketed GLP1RA products includes a Warning and Precaution for AKI. GLP1RA products are labeled for AKI because of postmarketing cases of serious AKI initially reported in patients using the first approved members of the class. The case narratives suggested AKI occurred in the setting of adverse GI reactions (nausea, vomiting, diarrhea), leading to dehydration and volume depletion. Because GI adverse reactions are caused by the GLP1RA class generally, FDA instituted class labeling for AKI. Although it is reasonable that GI AEs resulting in volume depletion could lead to infrequent events of AKI, an imbalance in such events was not observed for any other GLP1RA in randomized clinical trial data including large CVOTs, suggesting that the risk for AKI is greater with ITCA 650 than other GLP1RA agents. The higher risk observed in the preapproval database for ITCA 650 raises concern about the potentially greater risk versus other GLP1RA products in the postapproval setting: in the monitored setting of a clinical trial, some AKI may be prevented or mitigated, while this may not consistently occur in clinical practice. Moreover, the number of patients exposed to the ITCA 650 product would be much higher postapproval, and both of these factors differentiate the preapproval from the postapproval setting.

Summary of CDER's Conclusions on AKI

Although the number of AKI events in the ITCA 650 Phase 3 trials was small, CDER's analyses found an imbalance in overall and serious AKI events in subjects assigned to ITCA 650 versus comparator. For the more clinically relevant events of serious AKI, the data suggest an approximately 3 to 3.5-fold increased risk of serious AKI events among subjects treated with ITCA 650 versus comparators. The extent of the higher risk may be even more notable given the lower susceptibility of the ITCA FREEDOM population versus other CVOTs given the lower number of CKD patients in FREEDOM. Most serious AKI events among subjects who received ITCA 650 were preceded by GI symptoms. In the context of the device and PK exposure data demonstrating the potential for abrupt increases in exenatide exposures that could reasonably cause GI AEs leading to dehydration and AKI, CDER concluded the AKI signal could plausibly be related to treatment with ITCA 650. It is possible that the imbalance reflects a random occurrence; however, the issue should be addressed via submission of additional premarket clinical data to demonstrate that ITCA 650 is not associated with excess AKI risk.

3.3.2.3 MACE

Background

Patients with T2DM experience a two-to-threefold increased risk of atherosclerotic disease (Kannel and McGee 1979). Given the well-established relationship between diabetes and the adverse CV events of MI, stroke, and CV death, the assessment of CV safety is a focus of clinical development programs for all antihyperglycemic agents for the treatment of patients with T2DM. In the regulatory context, adequate information to assess CV safety of antihyperglycemic products is a key factor informing the benefit-risk assessment and regulatory-decision making for drugs to treat T2DM.

Based upon data from earlier diabetes drug programs showing unfavorable imbalances in MACE, FDA issued a guidance for industry (December 2008) (now withdrawn) recommending that all development programs for new antidiabetic therapies for T2DM rule out unacceptable CV risk prior to marketing. This guidance, which stated the premarket safety data should show that the upper bound of the two-sided 95% CI for the estimated risk ratio for important CV events is less than 1.8 (i.e., excludes an 80% increase), was in effect throughout the ITCA 650 development program and the CV risk assessment plan for the product included a prespecified analysis intended to exclude an 80% increase in important CV events among subjects treated with ITCA 650. At the time the guidance was issued, no antidiabetic therapy had demonstrated CV benefit, and it was expected that the true HR for a drug to provide glycemic control in patients with diabetes would be 1.0 (i.e., it was not anticipated

that the drug would have an effect on CV outcomes, either favorable or unfavorable). Given results from CVOTs across the GLP1RA class, our current understanding is that an HR of 0.8 to 0.9 would be anticipated (i.e., favorable effect on CV outcomes), as discussed further below.

The guidance included language explaining that unfavorable trends in MACE can present a concern: "Regardless of the method used, sponsors should consider the entire range of possible increased risk consistent with the confidence interval and the point estimate of the risk increase. For example, 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." These statements convey that even for antidiabetic products whose safety programs were able to exclude a 1.8 upper risk margin, concerning trends may warrant collection of additional premarket CV safety data to evaluate CV risk of a product.

The ITCA 650 clinical development program was designed, based on CDER advice, to meet the provisions set forth in the 2008 CV guidance (see Table 34). All suspected CV endpoints in the Phase 3 trials were reviewed and adjudicated by an independent CV endpoint adjudication committee, and the Applicant conducted a dedicated premarket, event-driven CVOT in a population enriched for risk of CV events (Study CLP-107) (Section 3.3).

CV Endpoints

In the ITCA 650 clinical development program, individual adjudicated endpoints for MACE were CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina (UA). The Applicant designated 4-point MACE (CV death, MI, nonfatal stroke, and UA) as the primary composite CV variable and 3-point MACE (CV death, MI, and nonfatal stroke) as a secondary composite CV variable in their CV safety analyses.[5] Prior to unblinding the results, the Applicant proposed numerous complementary analyses to evaluate the aggregate MACE data, consistent with advice provided by CDER. The Applicant's proposals for analyzing the MACE data were generally similar to those of other development programs of new antidiabetic agents designed to satisfy the requirements of the December (2008) guidance.

The Applicant analyzed the following endpoints for the aggregate MACE data:

1. Time to first occurrence of any event in the 4-point MACE composite endpoint (primary endpoint)
2. Time to first occurrence of any event in the 3-point MACE composite endpoint (secondary endpoint)

The following pooling strategies and censoring rules were used to analyze 4-point and 3-point MACE:

- Analyses conducted for pooled MACE data from CLP-107, CLP-103, CLP-105
  - 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")

[5] The Applicant referred to 4-point MACE as "MACE1" and 3-point MACE as "MACE2" in their analyses. For clarity, throughout this Briefing Document the terms 4-point MACE and 3-point MACE are used.

- Analyses conducted for CLP-107 individually (the large event-driven CVOT conducted in a population at high risk of MACE)
  - Analysis of all positively adjudicated events that occurred at any time during study participation (EOS or "On-Study censoring")
  - Analysis of all positively adjudicated events that occurred up to 30 days after discontinuation of ITCA 650/placebo ("EOT + 30 days" or "On-Treatment + 30 days censoring")
  - Analysis of all positively adjudicated events that occurred prior to discontinuation of ITCA 650/placebo (EOT or "On-Treatment censoring").

The use of composite MACE endpoints and Cox proportional hazard models to evaluate time to first event has become a standard approach to assessing CV risk in diabetes trials. Trials have varied somewhat in the selection of the components of the MACE composite, with most CVOTs using 3-point MACE as the composite primary outcome (Chilton et al. 2020). The primary advantage of using 4-point MACE rather than 3-point MACE is that it increases the overall event rate, thereby increasing the feasibility of conducting an event-driven trial (FREEDOM was designed to continue until 124 positively adjudicated events were collected across FREEDOM, CLP-103, and CLP-105). The primary disadvantage of using 4-point MACE rather than 3-point MACE is that the diagnosis of UA has a higher likelihood of unreliable event ascertainment relative to CV death, nonfatal MI, and nonfatal stroke (Kristensen et al. 2022). The consequence is that noise is introduced, diluting estimates of the treatment effect.

Other CV outcome variables assessed as endpoints included: first occurrence of any event in the composite endpoint of all-cause mortality, nonfatal MI, or nonfatal stroke; individual endpoint of CV death; individual endpoint of nonfatal MI; individual endpoint of nonfatal stroke; individual endpoint of hospitalization for UA; all-cause mortality.

Pooling Strategy

The Applicant conducted analyses of the pooled MACE data accrued in the Phase 3 glycemic control trials (CLP-103 and CLP-105) and the dedicated CVOT (CLP-107). This approach offered certain potential advantages, i.e., a larger number of events results in increased statistical power, and pooled analyses use all available data. For the planned pooled analyses in the ITCA 650 program, similar event ascertainment strategies were used (e.g., adjudication), reducing one potential source of noise. However, pooling CV event data from Studies CLP-103 and CLP-105 with CV data from Study CLP-107 has limitations because of differences in the enrolled trial populations and study designs. Studies CLP-103 and CLP-105 enrolled younger, healthier subjects with T2DM and were not enriched for CV risk, whereas Study CLP-107 enrolled older subjects with T2DM who were at higher CV risk. There was differential follow-up due to study designs utilizing a fixed study endpoint in CLP-103 and CLP-105 (i.e., A1C at 6 months) whereas Study CLP-107 was an event-driven trial. Thus, the most robust analysis of CV risk is assessed by examining Study CLP-107 (FREEDOM) because it enrolled the highest risk population for CV events and had the longest follow-up duration; for these reasons, CDER's additional CV risk analyses focused on FREEDOM alone.

Censoring Schemes

The prespecified primary analysis to satisfy the December (2008) CV guidance was the EOS pooled analysis of 4-point MACE. Furthermore, the prespecified primary endpoint of Study CLP-107 was the time-to-first occurrence of any event in the 4-point MACE composite endpoint based on an EOS analysis. In addition, the Applicant conducted sensitivity analyses of 4-point MACE and 3-point MACE using the pooled studies and Study

CLP-107[6]. These analyses were consistent with CDER's advice in an August 31, 2012 Advice Letter stating that CV safety analyses should be conducted using three separate censoring schemes for the primary and major secondary analyses (i.e., censoring all subjects at the time of first event, dropout, or end of treatment ("On-Treatment + 0"); censoring subjects at time of first event, dropout or 30 days after the end of treatment ("On-Treatment + 30"); and censoring subjects at the time of first event, dropout, or the end of study ("On-study"); see regulatory history in Section 5.3).

Both "On-Study" and "On-Treatment" analyses are important, as they have complementary strengths and weaknesses. An "On-Study" analysis preserves the principle of randomization by following an intent-to-treat approach, where all observed events are counted. However, "On-Study" estimates may be diluted if subjects continue to be followed for an extended period after treatment discontinuation. "On-Study" analyses include events that occur after the investigational product has been stopped (and may therefore be less likely to have caused the event, depending on the biology underlying the causal relationship between the treatment and the effect). As a consequence, "On-Study" analyses may underestimate treatment effects that are closely temporally linked to treatment exposure (e.g., hypersensitivity reactions that occur immediately after treatment exposure and are unlikely to occur after treatment discontinuation when subjects are still undergoing "On-Study" follow-up evaluations). Therefore, "On-Study" analyses may estimate a parameter closer to the null value in noninferiority studies. This point is key for assessments of safety, because "On-Study" analyses may underestimate the magnitude of risk that is temporally linked to treatment exposure. For these reasons, CDER also requested the Applicant submit analyses based on alternative censoring schemes to interrogate the data and assess whether a CV safety signal was observed (i.e., an "On-Treatment" analysis). An "On-Treatment" analysis includes only events that occur while the subject is exposed to the investigational product up to some predefined time period (e.g., 0 days, 7 days, or 30 days). "On-Treatment" analyses are informative because they estimate a treatment effect that is more closely linked to treatment *exposure* than "On-Study" analyses; however, such analyses introduce the potential for bias due to post-randomization confounding, because reasons for treatment discontinuation may differ across treatment arms and because follow-up times may differ across treatment groups. Therefore, whereas "on-study" analyses have the potential to estimate a parameter closer to the null in some cases, bias in "on-treatment" analyses due to post-randomization confounding may result in either overestimation or underestimation of the treatment effect (Wang et al. 2015; Yang et al. 2019).

Results of CV Safety Analyses

Key analyses that informed CDER's assessment of CV risk are presented and discussed below. Section 5.1 contains the results of additional CV analyses (including additional Kaplan-Meier curves) that CDER also considered in its assessment of CV risk.

The Applicant's prespecified primary endpoint of the time to first occurrence of any event in the 4-point MACE composite endpoint based on the pooled analysis of CLP-103, CLP-105, and CLP-107, using "On-Study" censoring was numerically unfavorable to ITCA 650: HR (95% CI) of 1.12 (0.83, 1.51). The same analysis for the 3-point MACE composite endpoint was also numerically unfavorable to ITCA 650: HR (95% CI) of 1.13 (0.83, 1.54).

[6] CLP-107 Clinical Study Report.

Table 18. Time to First Occurrence of 3-Point MACE (CV Death, Nonfatal MI, Nonfatal Stroke) and 4-Point MACE (CV Death, Nonfatal MI, Nonfatal Stroke, Unstable Angina) – ITT Population End of Study, Pooled Analysis of CLP-103, CLP-105, and CLP-107

MACE Type	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*	85/2649 (3.2%) 2.47	75/2502 (3.0%) 2.25	1.13 (0.82, 1.54)
4-Point MACE	96/2649 (3.6%) 2.80	85/2502 (3.4%) 2.56	1.12 (0.84, 1.50)

Source: CDER Review staff. Analysis: R v. 4.2 (MACE.R); data: adef.xpt from SDN0000.
* One hundred sixty positively adjudicated 3-point MACE events (154 in FREEDOM, 6 in glycemic control trials).
** Based on a Cox proportional hazards regression model. The primary analysis was conducted using a 95.4% confidence interval as it was part of a repeated testing plan.
Abbreviations: CV, cardiovascular; HR, hazard ratio; IR, incidence rate; ITCA 650, exenatide in DUROS device; ITT, intent-to-treat; MACE, major adverse cardiovascular event; MI, myocardial infarction; PY, patient-years

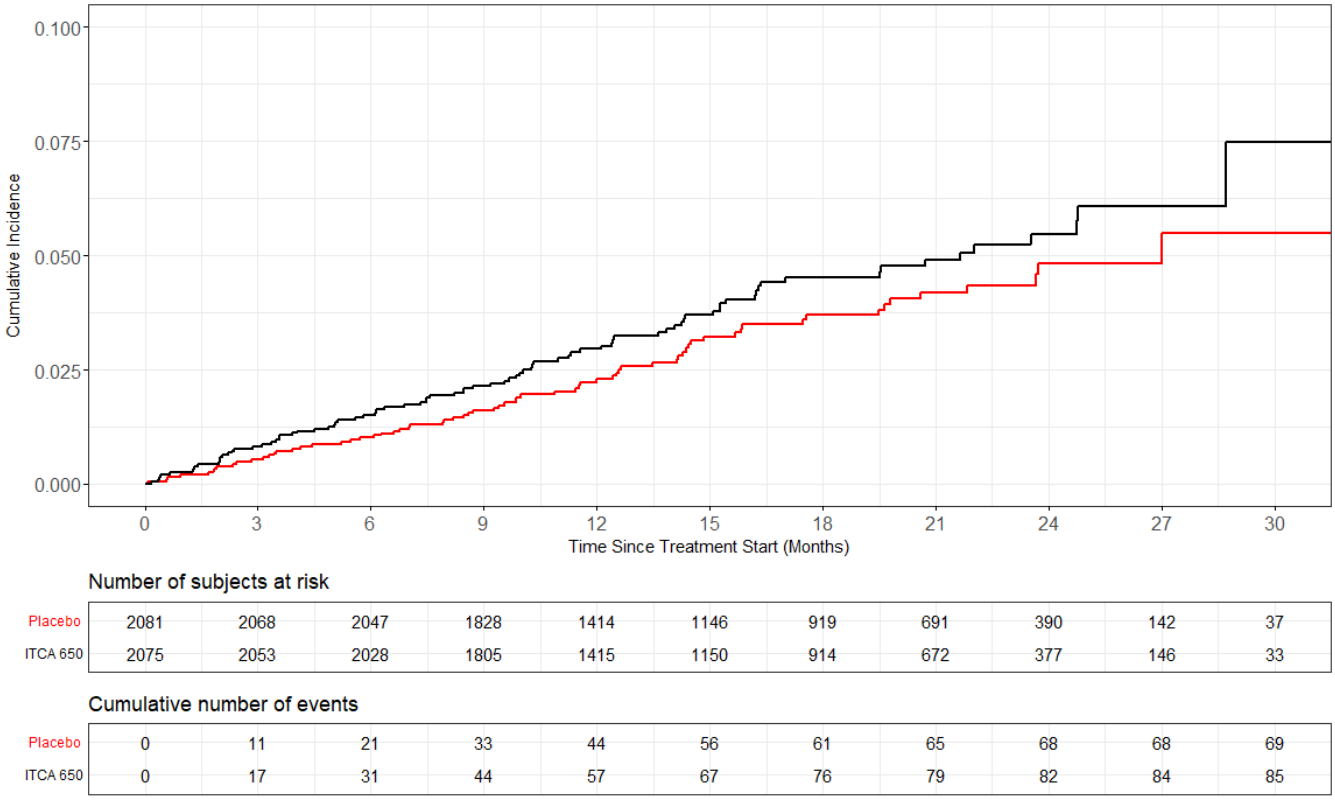
The results from FREEDOM suggest greater CV risk in a trial population enriched for CV events, as reviewed below. CDER assessed the results for the endpoint of the time to first occurrence of any event in the 3-point and 4-point MACE composite endpoints based only on events from CLP-107 (FREEDOM) using "On-Study" (EOS) censoring (Table 19). The results were a HR (95% CI) of 1.24 (0.90, 1.70) and 1.21 (0.90, 1.63), respectively. These 3-point MACE results provide an estimated increased risk of 24% and fail to exclude an increased risk of 70%. Estimates of CV risk were higher in the key subgroups of subjects ≥65 years of age, in whom the lower bound of the 95% CI nominally excluded 1 for 3-point and 4-point MACE, and subjects with baseline moderate renal impairment (Table 20). These subgroups may be more susceptible to a drug effect that increases CV risk.

Table 19. Time to First Occurrence of 3-Point MACE (CV Death, Nonfatal MI, Nonfatal Stroke) and 4-Point MACE (CV Death, Nonfatal MI, Nonfatal Stroke, Unstable Angina) – ITT Population End of Study, FREEDOM (CLP-107)

MACE Type	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*	85/2075 (4.1%) 2.94	69/2081 (3.3%) 2.37	1.24 (0.90, 1.70)
4-Point MACE	95/2075 (4.6%) 3.29	79/2081 (3.8%) 2.72	1.21 (0.90, 1.63)

Source: CDER Review staff. Analysis: R v. 4.2 (MACE.R); data: adef.xpt from SDN0000.
* One hundred fifty-four positively adjudicated 3-point MACE events.
** Based on a Cox proportional hazards regression model.
Abbreviations: CV, cardiovascular; HR, hazard ratio; IR, incidence rate; ITCA 650, exenatide in DUROS device; ITT, intent-to-treat; MACE, major adverse cardiovascular event; MI, myocardial infarction; PY, patient-years

Figure 13. Kaplan-Meier Plot for Time to First Occurrence of 3-Point MACE (CV Death, Nonfatal MI, Nonfatal Stroke)) – ITT Population End of Study, CLP-107 (FREEDOM)



Source: CDER Review staff; software: R v. 4.2; script: MACE_analysis.R; data: adef.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; HR, hazard ratio; ITCA 650, exenatide in DUROS device; ITT, intent-to-treat; MACE, major adverse cardiovascular event; MI, myocardial infarction

Table 20. Key Subgroup Analyses: Studies CLP-103, CLP-105 and CLP-107 Pooled Analyses and Study CLP-107 (FREEDOM)

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/1.73m^2				
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

The subgroup populations for age ≥65 years and eGFR <60 mL/min/1.73m^2 overlap moderately: in FREEDOM, 39.6% of subjects were at least 65 years old, 9.9% of subjects had baseline eGFR <60 mL/min/1.73m^2, and 5.7% of subjects were at least 65 years old and had baseline eGFR <60 mL/min/1.73m^2.

Notably, Table 21 demonstrates that at baseline, a smaller proportion of subjects enrolled in FREEDOM had moderate or severe renal impairment than the trial populations of any other CVOT in the class, and the proportion of subjects with baseline CV disease was lower relative to most of the other GLP1RA CVOTs. This observation is reflected in the lower incidence of MACE in the placebo arm of the trial compared to the placebo arms of the other trials (Table 22). As noted above, imbalances in MACE events unfavorable to ITCA 650 were most pronounced in susceptible subgroups (i.e., subjects ≥65 years of age, and subjects with baseline moderate-to-severe renal impairment), as interventions that increase risk of MACE cause the greatest harm among the highest-risk populations.

Table 21. Baseline Subject Characteristics 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**
Randomized subjects	14,752	4076	9340	3297	3183	9901	9463	4156	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/1.73 m^2 (%)	29	NR	35	30	29	27	30	30	23
eGFR 60-89 mL/min/1.73 m^2 (%)	49	NR	42	42	44	51	47	60	53
eGFR <60 mL/min/1.73 m^2 (%)	22	31	23	29	27	23	23	10	23

Source: CDER Review staff.

[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.

Abbreviations: 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

Table 22. 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)

Source: CDER Review staff.

[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.

Abbreviations: CI, confidence interval; CVOT, cardiovascular outcomes trial; GLP1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; MACE, major adverse cardiovascular event; NR, not reported

CDER also assessed 3-point and 4-point MACE in the ITCA 650 Phase 3 pooled studies and in Study CLP-107 alone using the alternative "On-Treatment + 30 days" and "On-Treatment + 0" (or simplified as "On-Treatment") censoring schemes (Table 23, Table 24, Table 31, and Table 32). Analyses using "On-Treatment" censoring including the "On-Treatment" analysis of FREEDOM, estimate a 36% increase in CV risk and allow for the possibility of an almost two-fold increase in CV risk based on the estimated HR and 95% CI: 1.36 (0.96, 1.92) (Table 24). These results are consistent with the analyses based on "On-Study" censoring presented above. As discussed above, however, "On-Treatment" analyses may estimate a treatment effect that is more closely linked to treatment exposure.

Table 23. Time to First Occurrence of 3-Point MACE (CV Death, Nonfatal MI, Nonfatal Stroke) and 4-Point MACE (CV Death, Nonfatal MI, Nonfatal Stroke, Unstable Angina) – ITT Population End of Treatment +30 Days, Pooled Analysis of CLP-103, CLP-105, and CLP-107

MACE Type	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*	77/2641 (2.9%) [2.51]	67/2493 (2.7%) [2.18]	1.18 (0.85,1.64)
4-Point MACE	86/2641 (%) [2.8]	77/2493 (%) [2.5]	1.14 (0.84, 1.56)

Source: Tables 15 and 16 of the CDER Safety Statistics Review (DARRTS August 11, 2017).

* One hundred sixty positively adjudicated 3-point MACE events (154 in FREEDOM, 6 in glycemic control trials).

** Hazard ratios were estimated based on a Cox model stratified by CV risk group and study with a fixed effect for treatment.

Abbreviations: CI, confidence interval; CV, cardiovascular; DARRTS, Document Archiving, Reporting, and Regulatory Tracking System; IR, incidence rate per 100 patient-years; ITT, intent-to-treat; MACE, major adverse cardiovascular event; MI, myocardial infarction; PY, patient-years

Table 24. Time to First Occurrence of 3-Point MACE (CV Death, Nonfatal MI, Nonfatal Stroke) and 4-Point MACE (CV Death, Nonfatal MI, Nonfatal Stroke, Unstable Angina) – ITT Population End of Treatment, FREEDOM (CLP-107)

MACE Type	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*	73/2070 (3.0%) [2.97]	56/2074 (2.9%) [2.26]	1.36 (0.96, 1.92)
4-Point MACE	82/2070 (4.0%) [3.4]	66/2074 (3.2%) [2.6]	1.29 (0.93, 1.79)

Source: Table 33 of the CDER Safety Statistics Review (DARRTS August 11, 2017).

* One hundred fifty-four positively adjudicated 3-point MACE events in FREEDOM.

** Hazard ratios were estimated based on a Cox model stratified by CV risk group with a fixed effect for treatment.

Abbreviations: CI, confidence interval; CV, cardiovascular; DARRTS, Document Archiving, Reporting, and Regulatory Tracking System; IR, incidence rate per 100 patient-years; ITT, intent-to-treat; MACE, major adverse cardiovascular event; MI, myocardial infarction; PY, patient-years

Analyses of the individual CV endpoints in FREEDOM demonstrated that the difference in 3-point and 4-point MACE between treatment arms was driven by events of CV death and nonfatal MI, while nonfatal stroke was neutral (Table 25, Table 26, and Table 27).

Table 25. Time to CV Death* – ITT Population With Three Methods of Censoring

Time Point	ITCA 650 Number of Events/Total No. (%) IR (n/100 PY)	Control Number of Events/Total No. (%) IR (n/100 PY)	HR (95% CI)**
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)

Source: CDER Review staff. Analysis: R v. 4.2 (MACE.R); data: adef.xpt from SDN0000.

* Fifty-one positively adjudicated CV deaths in FREEDOM.

** Based on a Cox proportional hazards regression model.

Abbreviations: CI, confidence interval; CV, cardiovascular; IR, incidence rate per 100 patient-years; ITT, intent-to-treat; MI, myocardial infarction; PY, patient-years

Table 26. Time to First Occurrence of Nonfatal MI* – ITT Population With Three Methods of Censoring

Time Point	ITCA 650 Number of Events/Total No. (%) IR (n/100 PY)	Control Number of Events/Total No. (%) IR (n/100 PY)	HR (95% CI)**
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)

Source: CDER Review staff. Analysis: R v. 4.2 (MACE.R); data: adef.xpt from SDN0000.

* Fifty-five positively adjudicated nonfatal MIs in FREEDOM.

** Based on a Cox proportional hazards regression model.

Abbreviations: CI, confidence interval; IR, incidence rate per 100 patient-years; ITT, intent-to-treat; MI, myocardial infarction; PY, patient-years

Table 27. Time to First Occurrence of Nonfatal Stroke* – ITT Population With Three Methods of Censoring

Time Point	ITCA 650 Number of Events/Total No. (%) IR (n/100 PY)	Control Number of Events/Total No. (%) IR (n/100 PY)	HR (95% CI)**
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)

Source: CDER Review staff. Analysis: R v. 4.2 (MACE.R); data: adef.xpt from SDN0000.

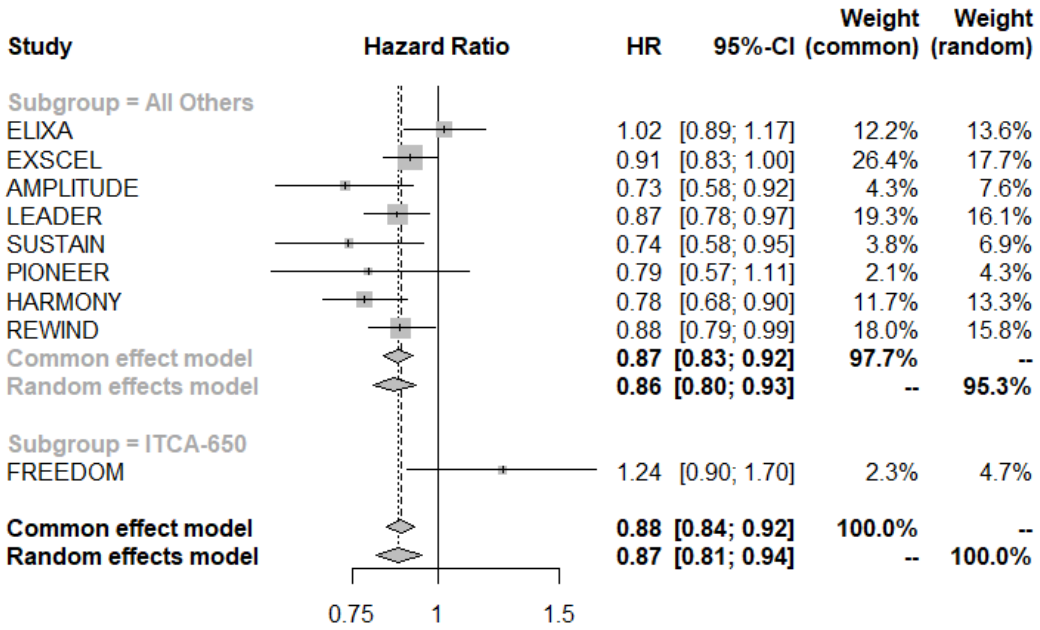
* Forty-six positively adjudicated nonfatal strokes in FREEDOM.

** Based on a Cox proportional hazards regression model.

Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate per 100 patient-years; ITCA 650, exenatide in DUROS device; ITT, intent-to-treat; PY, patient-years

CDER also conducted a meta-analysis for 3-point MACE including results of the published CVOTs of marketed GLP1RA products, plus AMPLITUDE (efpeglenatide) and FREEDOM, and found that ITCA 650 appears different from other products in the GLP1RA class with respect to CV outcomes (Figure 14). The CDER meta-analysis calculated results using both a common effect model (HR=0.87; 0.83 to 0.92) and a random effects model (HR=0.86; 0.80 to 0.93); the two statistical approaches yielded nearly identical results. CDER notes that the individual CVOT results for all of the other long-acting GLP1RAs are consistent with the overall estimate based on the meta-analysis: the point estimate for the HR for 3-point MACE of each of these seven CVOTs is near or below the point estimates of the meta-analysis. The results of ELIXA, the short-acting once-daily GLP1RA lixisenatide CVOT which was conducted in a different patient population (subjects with recent history of an acute coronary syndrome event) was the only other trial that did not show evidence of benefit. CDER concluded that the result for ITCA 650 in FREEDOM (4-point MACE HR=1.24; 0.90 to 1.70) is an outlier based on a statistical comparison with other CVOTs. The lower bound of the 95% CI (0.90) was higher than the point estimate for long-acting GLP-1RA agents (0.87 or 0.86) based on the meta-analysis as well as higher than any individual estimated HR other than ELIXA.

Figure 14. Meta-Analysis of 3-Point MACE Across CVOTs in the GLP1RA Class



Test for subgroup differences (common effect): $\chi^2_1 = 4.53$, df = 1 ($p = 0.03$)
Test for subgroup differences (random effects): $\chi^2_1 = 4.78$, df = 1 ($p = 0.03$)

Source: CDER Review staff. R v. 4.3, using the R Package 'meta' (Balduzzi et al. 2019); Data derived from Table 22.
Abbreviations: CI, confidence interval; EOS, end of study; HR, hazard ratio; ITCA 650, exenatide in DUROS device MACE, major adverse cardiovascular event

The results of CDER's meta-analysis are similar to those reported in several recently published meta-analyses of CVOTs in the GLP1RA class (Giugliano et al. 2021). A meta-analysis including CVOT results from the marketed GLP1RAs plus FREEDOM estimates an HR for MACE of 0.87 (95% CI: 0.81, 0.94) and states that "the FREEDOM results appear dissimilar to prior GLP-1 receptor agonist trials."(Lee et al. 2022).

Finally, CDER conducted a meta-analysis for all-cause mortality including results of the published CVOTs of marketed GLP1RA products, plus AMPLITUDE and FREEDOM, with dissimilar observations for ITCA 650 compared with the GLP1RA class (Figure 23). The CDER analysis confirmed the findings of the published meta-analyses that have previously reported that the data from the CVOTs of other GLP1RA show a reduction in all-cause mortality: the common effect model and the random effects model both yielded an all-cause mortality of HR 0.88 (95% CI: 0.83 to 0.93) for the eight published CVOTs other than FREEDOM. The meta-analysis by (Lee et al. 2022) based on the same CVOTs reported the same results for all-cause mortality: HR 0.88 (95% CI: 0.82 to 0.94). Notably, the all-cause mortality HR for EXSCEL (the CVOT for the approved long acting exenatide product Bydureon) was 0.86 (95% CI: 0.77 to 0.97). By contrast, for FREEDOM, the observed all-cause mortality HR is 1.20 (95% CI: 0.79 to 1.81).

Conclusions on MACE

The primary and secondary endpoint analyses and all other prespecified analyses of CV risk, regardless of pooling or censoring strategy utilized, support the same conclusion: the 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. The observation, that

FREEDOM is an outlier among the many other long-acting GLP-1RA CVOTs also fails to provide reassurance that ITCA 650 is not associated with an increase in CV risk.

Overall, in the context of the IVR and PK data and other unfavorable imbalances in clinical outcomes (i.e., AKI, all SAEs, all-cause mortality), as well as the larger context of the GLP1RA class in which several products have demonstrated CV benefit, CDER interprets the MACE data from FREEDOM to constitute a CV signal that requires additional premarket investigation to ensure patients treated with the product are not exposed to excess CV risk.

3.3.2.4 SAEs

In clinical trials, an SAE is defined as any untoward medical occurrence associated with the use of a drug, whether or not considered drug-related, that results in: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, and/or a congenital anomaly/birth defect (21 CFR 212.32[a]).

In addition, important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

In FREEDOM, subjects randomized to ITCA 650 experienced a numerically higher incidence of SAEs than subjects randomized to the placebo control. The total number of patients experiencing at least one SAE was 369 of the 2070 subjects randomized to ITCA 650 (17.8%), compared to 324 of the 2074 subjects randomized to placebo (15.6%). The imbalance not favoring ITCA 650 was driven by differences in SAEs classified as GI disorders, renal and urinary disorders, vascular disorders, and general disorders and administration site conditions (according to MedDRA System Organ Class categories). The MedDRA high-level terms (HLTs) from those system organ class categories with imbalances not favoring ITCA 650 and at least 5 SAE events include: “peripheral vasoconstriction, necrosis, and vascular insufficiency” (14 versus 8), “renal lithiasis” (6 versus 1), “renal failure and impairment” (12 versus 5), “death and sudden death” (13 versus 5), and “acute and chronic pancreatitis” (7 versus 1).

Given the observed imbalance in total subjects experiencing an SAE and total SAEs experienced, CDER conducted a hazard ratio analysis for the outcome of “time to first SAE.” Whether an “end of study” or “end of treatment” censoring strategy was applied, the analyses showed a nominally statistically significant increased risk of SAE among subjects who received ITCA 650 compared to placebo (Table 28).

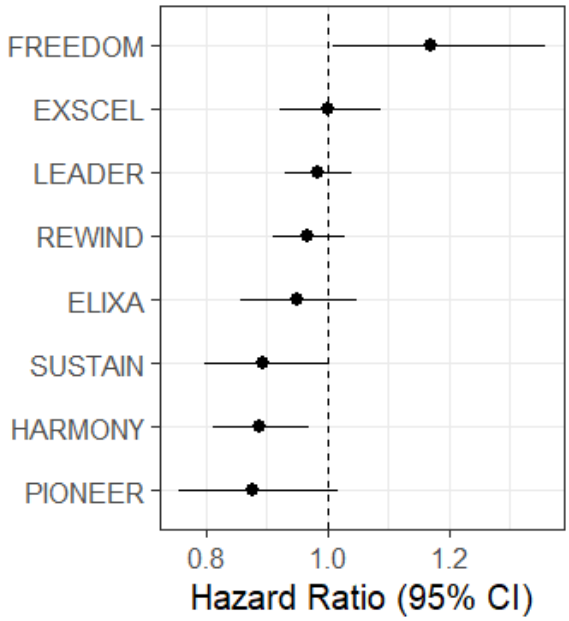
Table 28. Time-to-First SAE (Fatal and Nonfatal), FREEDOM, EOT + 30 Days and EOS

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; software: R v. 4.2; script: SAE analysis R; data: adsl.xpt and adae.xpt, SDN0000
Abbreviations: CI, confidence interval; EOS, end of study; ITCA 650, exenatide in DUROS device; IR, incidence rate; PY, patient-years

Although increase in the incidence of SAEs in FREEDOM is relatively modest, this contrasts with observations from other GLP1RA products where a trend towards reduced incidence of SAEs is observed. This is shown in Figure 15.

Figure 15. Time to First Occurrence of SAE (Fatal and Nonfatal) in GLP1RA CVOTs, On-Study



Source: CDER Review staff; software: R v. 4.2; script: SAE analysis R; data: curated from NDA 209053 (adsl.xpt and adae.xpt, SDN0000) and confidential commercial information from other NDA/BLAs.
HR estimated using marginal cox proportional hazards model with treatment (GLP1RA or comparator) as a fixed effect.
On-study analysis.
Abbreviations: BLA, biologics license application; CVOT, cardiovascular outcomes trial; EOS, end of study; GLP1RA, glucagon-like peptide 1 receptor agonist; HR, hazard ratio; NDA, new drug application; SAE, serious adverse event

3.3.2.5 Device Complications

The device-related complications included 'Assisted removals' – events where the subject needed to be referred to a surgeon or interventional radiologist to remove the device, and insertion site AEs including 'Site infections' – events where the subject developed an infection at the device insertion site requiring medical intervention (typically including a course of antibiotics), 'Hemorrhage' – events where the subject experienced clinically significant bleeding secondary to the device placement and/or removal, and 'Extrusions' – events where the device was spontaneously expelled from the subject (these include events that were observed by the subject as well as events that were only discovered during follow-up with the health-care provider).

Assisted Removals

The most frequent device related complication was the need for medical imaging and referrals to surgeons or interventional radiologists to remove the implanted ITCA 650 device. In the ITCA 650 development program, a total of 5134 subjects underwent 20,701 procedures (including 5134 initial placement procedures, 10,538 removal/replacement procedures, and 5029 final removal procedures) of either ITCA 650 exenatide or placebo devices. The removal procedures were generally done by trained healthcare providers at the clinic sites and required only palpation and incision to successfully remove the device. However, a total of 165 imaging procedures (most frequently x-ray or ultrasound, but also fluoroscopy, CT scan, and magnetic resonance imaging) were required to locate and/or assist in removal of the device. In most cases where imaging was required, the subject was referred to a surgeon or interventional radiologist to remove the device after the initial attempt at the clinical site had failed: a total of 163 device removals (1.1% of all removal procedures) required referral to a surgeon or interventional radiologist. Referrals to surgeons or interventional radiologists of

subjects who experienced failed attempts to remove the ITCA 650 device usually but not always resulted in a successful removal of the device on the first visit to the surgeon.

Insertion Site AEs

Of the 5134 subjects who underwent at least one device placement, 83 (1.6%) experienced an AE related infection of the placement site. The most common preferred terms to describe these were application site infection (54) and application site cellulitis (20). Only two of the events of application site infection were described as severe. In addition, five cases were classified as application site abscesses and one case as an abdominal abscess. None of the site infection events were reported as serious.

Of the 5134 subjects who underwent at least one device placement, 87 (1.7%) experienced application site hemorrhage. Application site bruising was also reported (72 of 5134 subjects or 1.4%). Only one of these events was reported as serious and that patient was using concomitant anticoagulation.

A total of 60 events of device extrusion were observed in the core clinical trials. This includes one event of a subject electing to remove the device without medical assistance. The rest of the events were spontaneous events of unintended discharges of the device from the body, usually witnessed by the subject but often only deduced when no device could be found at follow-up visits.

3.3.2.6 Adherence

Medication adherence is defined as the extent to which patients take treatments as prescribed. CDER acknowledges that adherence is a critical clinical issue in treatment of patients with T2DM and that improved adherence leading to improved long-term outcomes would be a benefit important to consider in the benefit risk assessment of a treatment. However, at this time there is insufficient evidence that ITCA 650 will lead to improved long-term outcomes over available GLP1RA therapies that require only weekly injections, sufficient to outweigh the identified and unresolved safety concerns with ITCA 650.

The Applicant posits that an implantable device will lead to increased treatment adherence because once implanted, the product does not require patients to take any action. T2DM, however, is a chronic condition that requires lifelong treatment. The ITCA 650 device needs to be exchanged every 6 months and the removal/replacement procedure is nontrivial, as it requires a clinic visit and medical procedure by a healthcare professional with specific training. Furthermore, the procedure, as detailed above, is associated with a nonzero rate of placement/removal failures and complications that have impact on patient preference. It cannot be assumed that patients will continue to receive treatment beyond the 6-month lifespan of the implanted device, long enough to have an advantage in terms of reduction of diabetes complications. Whether any increase in adherence that could potentially be seen long-term would translate to meaningful therapeutic benefits has not been demonstrated.

As detailed in Section 3.3, devices were removed early in 19.6% of subjects in CLP-103, 23.4% of subjects in CLP-105, and 17.8% of subjects in CLP-107 randomized to the ITCA 650 treatment arm – most commonly as the result of an AE associated with the device. In the only head-to-head trial utilizing an active comparator arm (sitagliptin), treatment discontinuation was in fact higher among subjects randomized to ITCA 650 compared with daily oral sitagliptin. Marketed long acting GLP1RA treatments only need to be injected once weekly further reducing burden on patients. Thus, it is not clear there would be a significant number of patients who would find a surgical procedure every 6 months less burdensome than a self-administered weekly injection.

The three pivotal clinical trials, all showed that: 1) subjects who received ITCA 650 discontinued treatment at higher rates than subjects who did not, 2) the most common reason for discontinuation of ITCA 650 was an AE

(including subjects presenting before scheduled procedures to either study sites or emergency facilities to have the device removed). All three pivotal studies used placebo devices, suggesting that the trial data may underestimate the true difference in treatment discontinuations compared to a nonimplantable treatment (as the observed difference across treatment arms do not reflect factors such as inconvenience, discomfort, and complications related to the device placement procedures).

No data outside of the clinical trials are available to elucidate how many patients would continue to have repeated placement of the device over years of treatment and the data from the clinical trials cannot inform completely the issue of adherence, as the behavior of subjects in clinical trials may differ from the behavior of patients in the real world (e.g., subjects who elect to enroll in clinical trials and who are working with study coordinators within the structure of a protocol may be more likely to adhere to medical instruction). However, the rates of treatment discontinuation in the real world would be expected to be higher than the rates of treatment discontinuation in the clinical trial setting.

3.4 Risk Mitigation

CDER considered whether labeling or risk mitigation beyond labeling, including requirements under a Risk Evaluation and Mitigation Strategy (REMS),[7] could sufficiently mitigate the observed risks of AKI and MACE. CDER did not identify any risk management strategies that could reduce the frequency of these observed events and render the benefit risk assessment favorable.

The Applicant has proposed to address the AKI risk through labeling, e.g., by limiting treatment with the product to patients with baseline eGFR ≥45 mL/min/1.73m^2 and recommending increased monitoring for GI symptoms during an initial time period, e.g., 30 days or 60 days after implantation, or providing labeling language informing of symptoms or laboratory findings that would trigger early device removal. However, CDER's review concluded that the risk of AKI cannot be adequately mitigated by labeling or a REMS, for the following reasons:

- Increased monitoring during a particular window would not successfully mitigate risk because although eight serious AKI events occurred within the first 30 days after a device placement or replacement, six events occurred at later timepoints after a device initial placement or replacement, ranging from 39 to >100 days. CDER concluded that there is 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 to inform prescribers and adequately mitigate the risk of AKI. Furthermore, this risk is reintroduced every time a new device is placed.
- Warning patients about symptoms and warning prescribers about laboratory values that should trigger early device removal may not be successful in mitigating risk because:
  - There is a requirement for a surgical procedure to remove the ITCA 650 device before exposure to the drug will stop. Review of the narratives of subjects admitted to hospitals with serious AKI events demonstrated that delays occurred in device removal even in the context of a monitored clinical trial in which subjects and investigators were advised of the potential risks. For example, two subjects did not undergo device removal until 4 and 2 days into their hospitalizations for AKI, respectively. In the case of

[7] Section 505-1 of the Food, Drug, and Cosmetic Act authorizes the FDA to require pharmaceutical sponsors to develop and comply with a Risk Evaluation and Mitigation Strategy (REMS) for a drug if FDA determines that a REMS is necessary to ensure that the benefits of the drug outweigh the risks. A REMS is a required risk management plan that uses risk minimization strategies beyond the professional labeling. The elements of a REMS can include: a Medication Guide or patient package insert, a communication plan to healthcare providers, certain packaging and safe disposal technologies for drugs that pose a serious risk of abuse or overdose, elements to assure safe use, and an implementation system.

another subject, who was admitted for dehydration and AKI in the setting of GI symptoms 75 days after device initiation, the device remained in place and the subject continued to have elevated creatinine clearance for more than 3 months before a consultant nephrologist recommended device removal. This subject's creatinine clearance was reported as being at baseline 12 days after device removal. Thus, 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.

- Prior to experiencing an AKI 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. CDER also notes that labeling advising the urgent removal of the device in a patient who experiences nausea or other GI symptoms is impractical, given the high frequency of occasional nausea both in healthy subjects, but especially in patients with T2DM receiving treatment with a GLP1RA.

Although not proposed by the Applicant, CDER considered whether labeling was a reasonable strategy to address the uncertainty around the CV risk assessment for the T2DM indication. Patients with T2DM are at increased risk for MACE including younger patients with T2DM who do not have known CV disease. Thus, CDER concluded that labeling ITCA 650 to limit use to a particular subpopulation of patients with T2DM (e.g., younger patients without a CVD diagnosis) would not adequately address the risk of MACE.

In summary, risk mitigation interventions through product labeling or a REMS could not be identified that would ensure the benefits outweigh the risks of ITCA 650.

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Guidances for Industry

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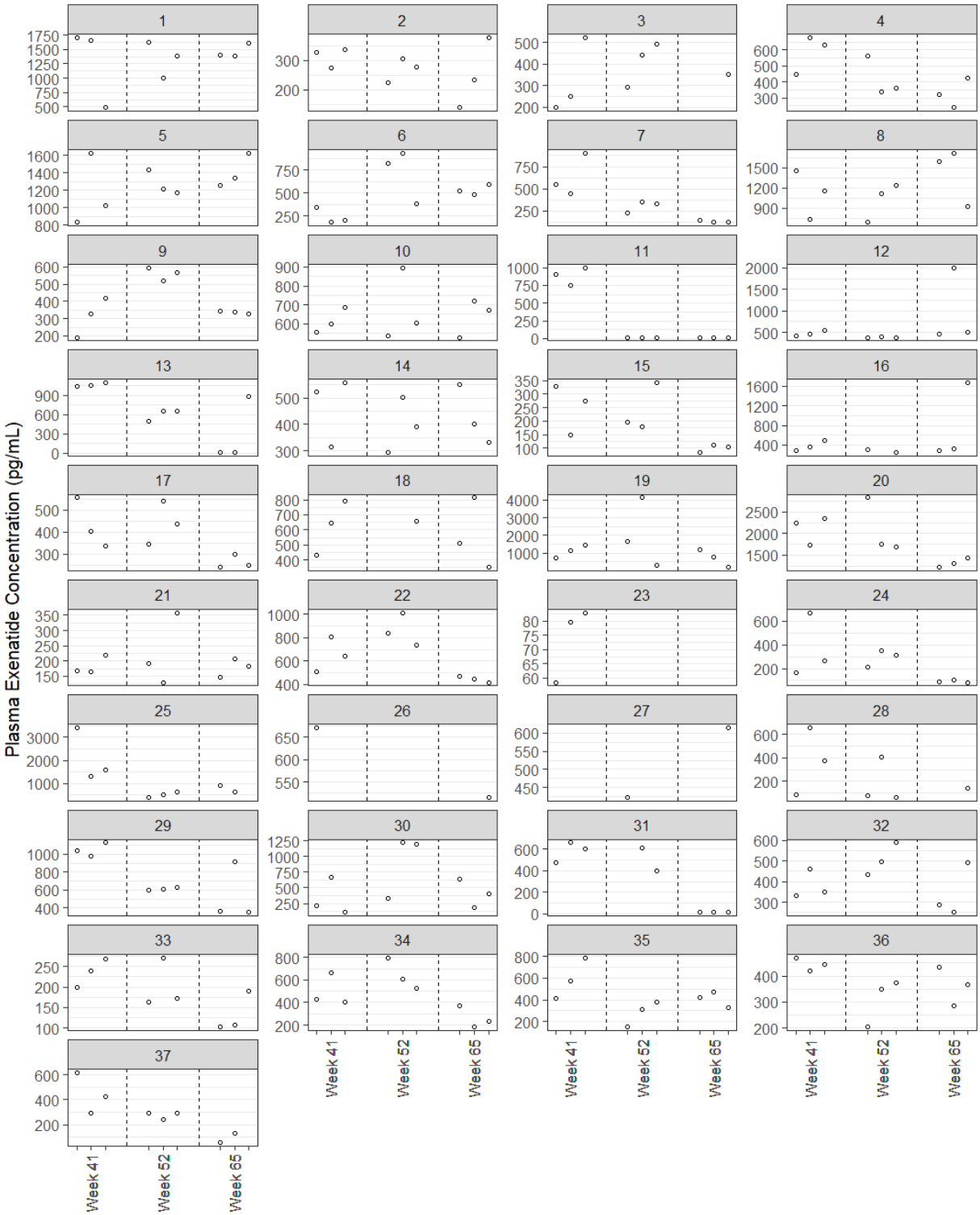
5 Appendix

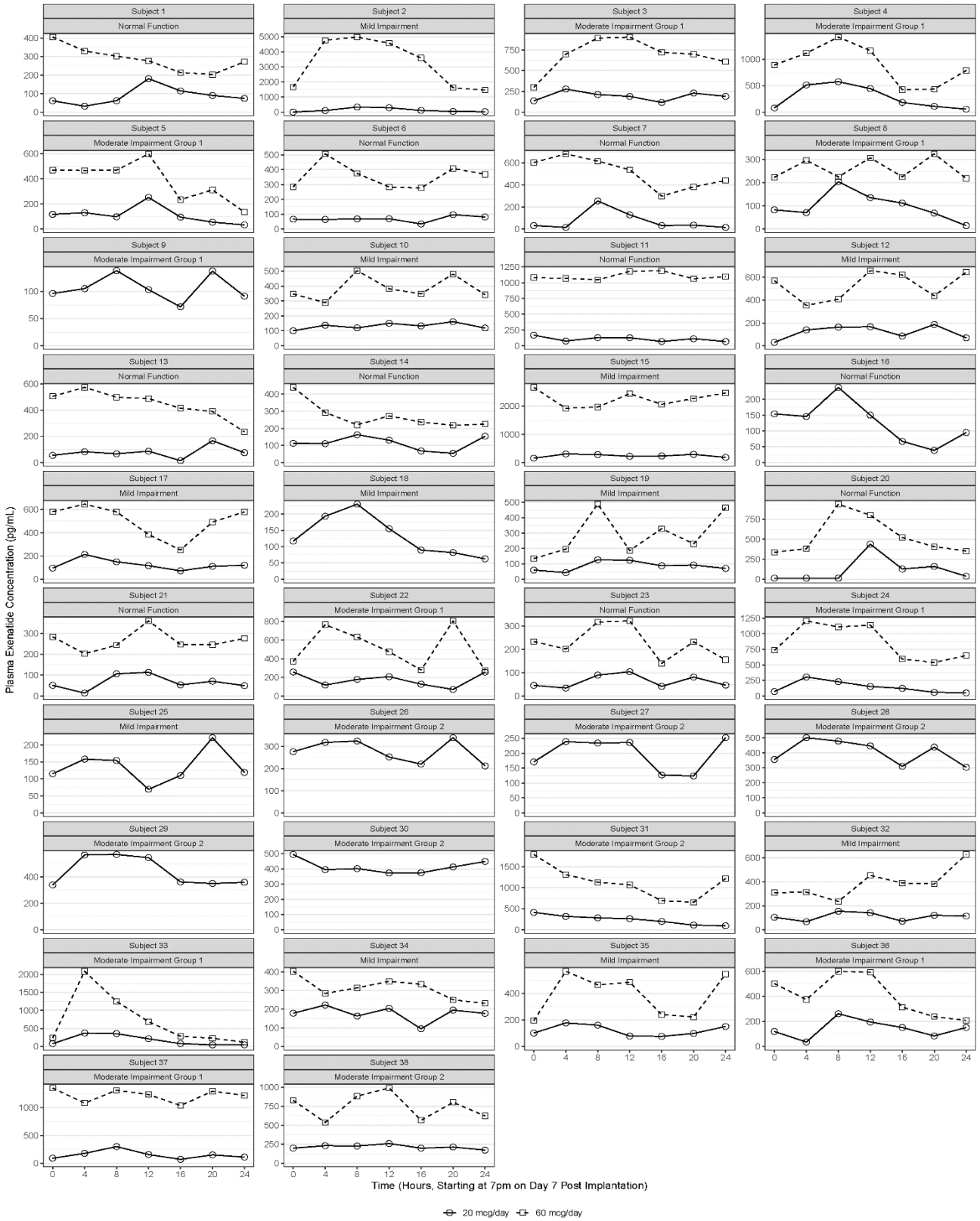
5.1 Additional In Vitro Release and Clinical Pharmacology Information

Figure 16. Individual Concentration vs. Time Profiles for ITCA 650 (Exenatide) in CLP-103SS



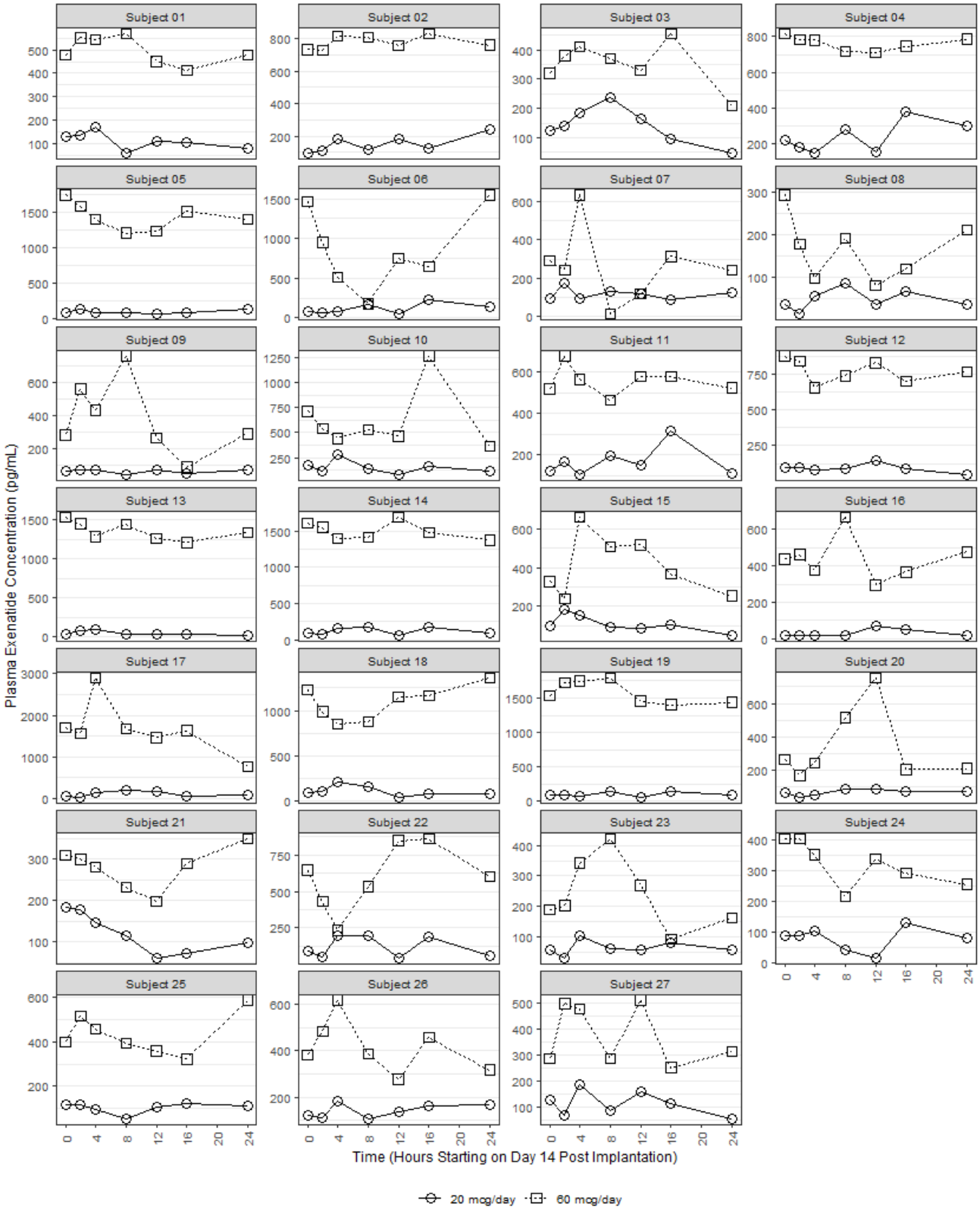
Source: CDER Review staff. Analysis: R v. 4.2. using sdtm (pc.xpt) from SDN0000.
Subject 11 was found to have a failed device upon removal after Week 65.

Figure 17. Individual Concentration vs. Time Profiles for ITCA 650 (Exenatide) in CLP-109



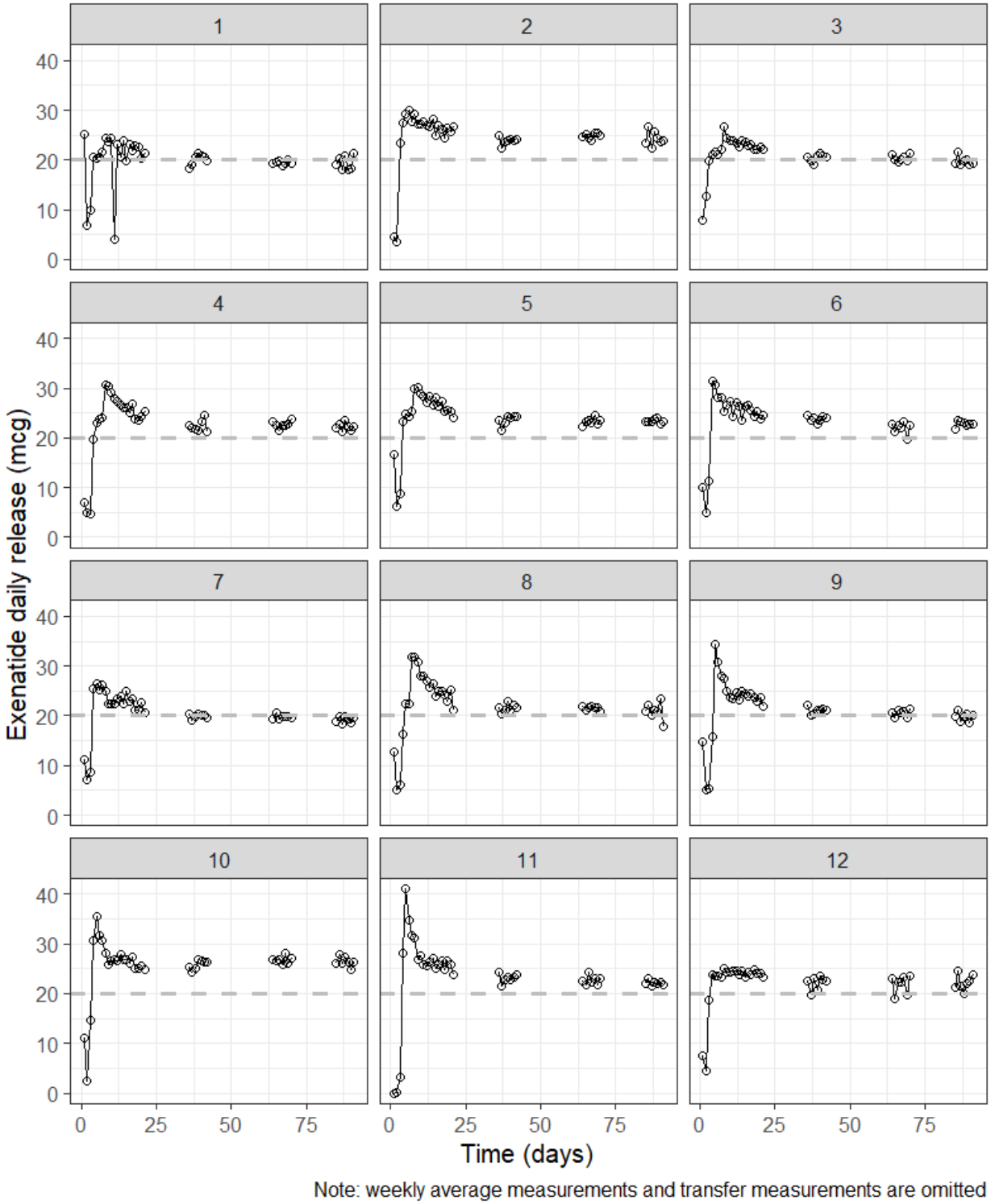
Source: CDER Review staff. Analysis: R v. 4.2. using sdtm (pc.xpt) from SDN0000.
Samples below the lower quantification of quantification (LLOQ) were imputed as LLOQ÷2.

Figure 18. Individual Concentration vs. Time Profiles for ITCA 650 (Exenatide) in CLP-116



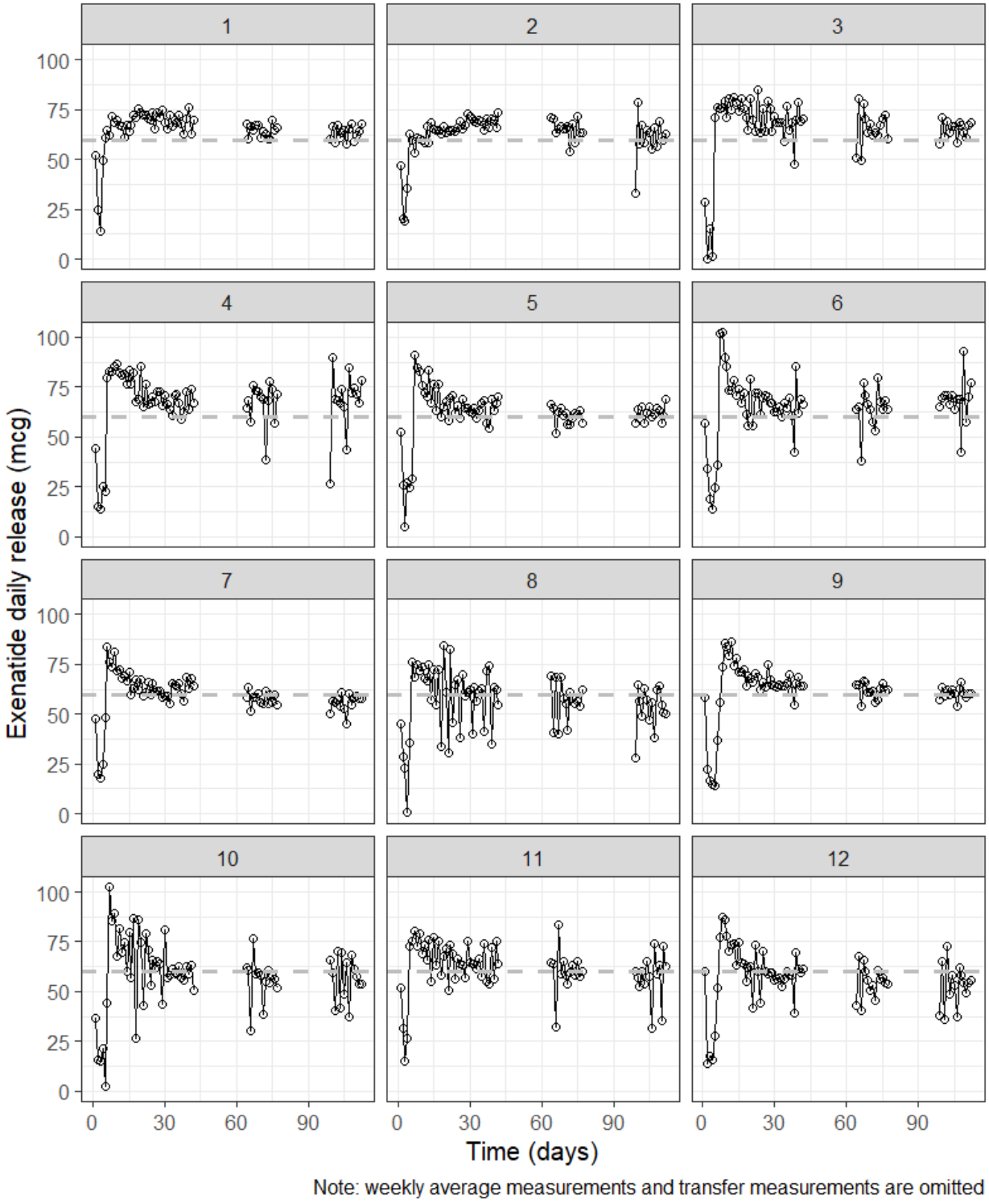
Source: CDER Review staff. Analysis: R v. 4.2. using sdtm (pc.xpt) from SDN0000.
Two subjects with no pharmacokinetic data were omitted. Samples below the lower quantification of quantification (LLOQ) were imputed as LLOQ÷2.

Figure 19. All Daily In Vitro Release Data From ITCA 650 20 mcg/Day Devices – Group A



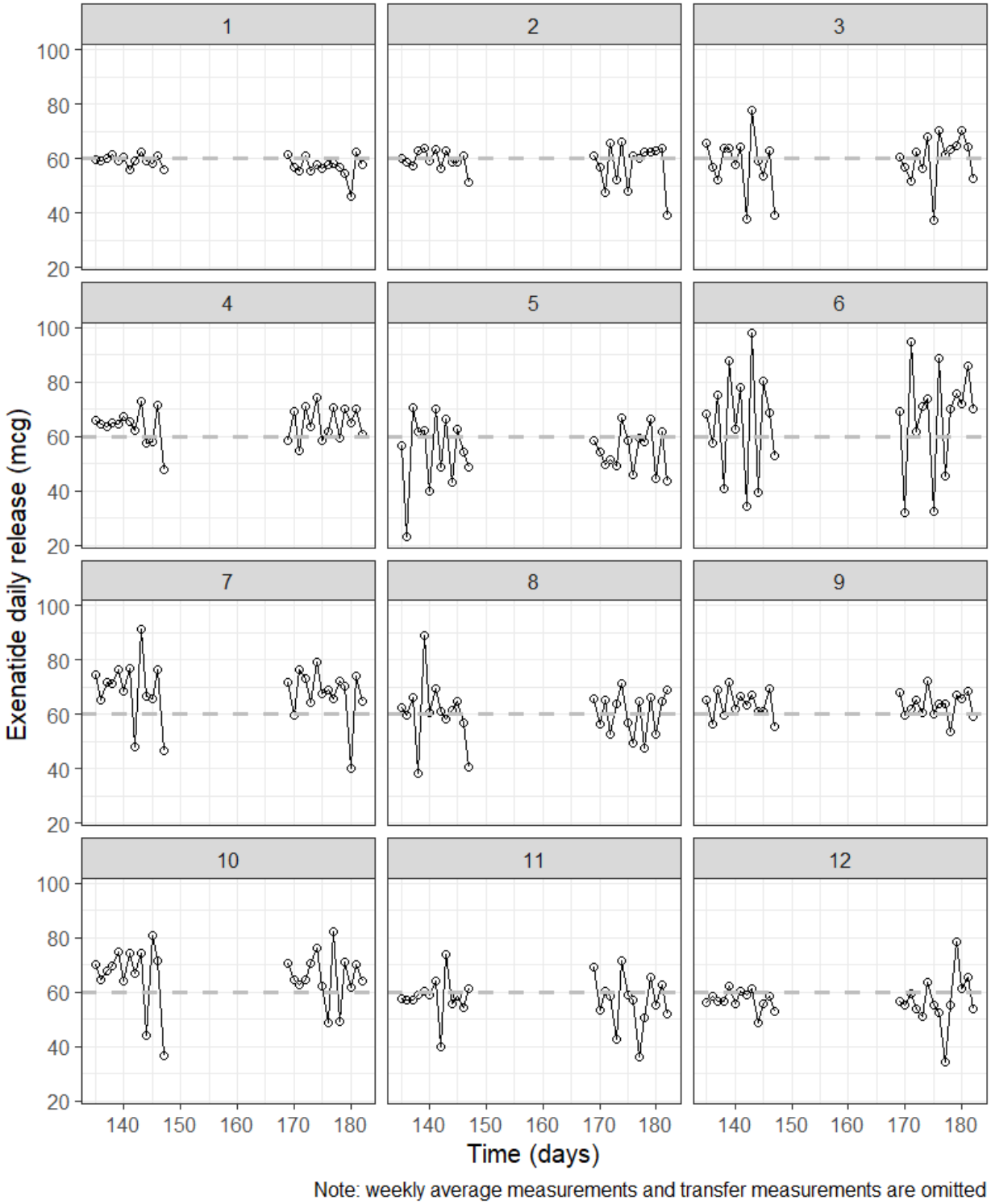
Source: CDER Review staff. Software: R v. 4.2 (IVC_plots.R); data adapted from Study VV 52888 (SDN0060).

Figure 20. All Daily In Vitro Release Data From ITCA 650 60 mcg/Day Devices – Group B



Source: CDER Review staff. Software: R v. 4.2 (IVC_plots.R); data adapted from Study VV 52888 (SDN0060).

Figure 21. All Daily In Vitro Release Data From ITCA 650 60 mcg/Day Devices – Group C



Source: CDER Review staff. Software: R v. 4.2 (IVC_plots.R); data adapted from Study VV 52888 (SDN0060).

5.2 Additional Clinical Information

Study CLP-107 Enrichment Strategy/Inclusion Criteria

- High-risk group defined as males and females ≥40 years old with at least one documented occurrence of CAD, cerebrovascular disease, or symptomatic peripheral arterial disease whose disease, in the Investigator's opinion, was stable and not in the acute recovery stage of a CV event (i.e., events listed below were to have occurred at least 1 month prior to screening, unless otherwise specified);
- Documented CAD – as defined by at least one of the following:
  - Confirmed history of myocardial infarction (MI) >3 months prior to screening; subjects with a history of unstable angina could qualify if ischemia had been documented by criteria below:
    - Documented angina pectoris with ischemic electrocardiogram (ECG) changes on a graded exercise test, or positive cardiac imaging stress test results documenting ischemia;
    - Angiographic or computed tomography (CT) imaging (e.g., multidetector CT/CT angiogram [MDCT/CTA]) evidence of at least 50% narrowing of one or more coronary arteries and subjects who had since undergone percutaneous or surgical revascularization;
  - Documented cerebrovascular disease – as defined by at least one of the following:
    - Confirmed history of ischemic stroke (documented by brain CT or magnetic resonance imaging)
    - Carotid ultrasound or angiographic evidence of at least 50% narrowing of one or more carotid arteries;
    - Carotid ultrasound or angiographic evidence of at least 50% narrowing of one or more carotid arteries and patients who had since undergone revascularization
  - Documented symptomatic peripheral arterial disease – as defined by at least one of the following:
    - Current intermittent claudication and ankle-brachial index ≤0.90 and/or documented peripheral artery disease with >50% stenosis;
    - History of intermittent claudication that required previous intervention (peripheral bypass, angioplasty)

OR

- Low-risk group defined as males and females ≥60 years old with at least one other risk factor in addition to T2D:
  - Duration of T2DM >10 years;
  - Smoking ≥15 cigarettes/day at Screening;
  - History of hypertension and taking antihypertensive medications to treat hypertension;
  - Family history of premature CAD (family members where CAD was observed in men <55 years of age and women <65 years of age);
  - Fasting low-density lipoprotein (LDL) cholesterol ≥100 mg/dL at Screening despite antilipidemic therapy for ≥3 months prior to Screening;
  - Fasting high-density lipoprotein (HDL) cholesterol <40 mg/dL at Screening;
  - Coronary calcium score >400;
  - History of documented diabetic nephropathy as evidenced by established microalbuminuria with a urinary albumin-creatinine ratio (ACR) ≥30 mcg/mg in a spot urine sample

Table 29. List of MedDRA Preferred Terms Used for Standardized MedDRA Queries and FDA Medical Queries

ARF SMQ N (MedDRA v. 18.1)	AKI FMQ N (FMQ v. 2.1)	ARF SMQ B (MedDRA v. 18.1)	AKI FMQ B (FMQ v. 2.1)
Acute kidney injury	Acute kidney injury	Acute kidney injury	Acute kidney injury
Acute phosphate nephropathy	Acute phosphate nephropathy	Acute phosphate nephropathy	Acute phosphate nephropathy
Acute prerenal failure	Acute prerenal failure	Acute prerenal failure	Acute prerenal failure
Anuria	Anuria	Albuminuria	Anuria
Azotaemia	Cardiorenal syndrome	Anuria	Azotaemia
Continuous haemodiafiltration	Continuous haemodiafiltration	Azotaemia	Blood creatinine abnormal
Dialysis	Crush syndrome	Blood creatinine abnormal	Blood creatinine increased
	Crystal nephropathy	Blood creatinine increased	Blood urea increased
Haemodialysis	Delayed foetal renal development	Blood urea abnormal	Blood urea nitrogen/creatinine ratio increased
Haemofiltration	Frasier syndrome	Blood urea increased	C1q nephropathy
Neonatal anuria	GRACILE syndrome	Blood urea nitrogen/creatinine ratio increased	Cardiorenal syndrome
Nephropathy toxic	Haemolytic uremic syndrome	Continuous haemodiafiltration	Continuous haemodiafiltration
Oliguria	Hepatorenal failure	Creatinine renal clearance abnormal	Creatinine renal clearance abnormal
Peritoneal dialysis	Nephritis	Creatinine renal clearance decreased	Creatinine renal clearance decreased
Prerenal failure	Nephropathy toxic	Creatinine urine abnormal	Crush syndrome
Renal failure	Oliguria	Creatinine urine decreased	Crystal nephropathy
Renal failure neonatal	Pancreatorenal syndrome	Crystal nephropathy	Delayed foetal renal development
Renal impairment	Postoperative renal failure	Dialysis	Dialysis
Renal impairment neonatal	Postrenal failure	Fractional excretion of sodium	Frasier syndrome
	Prerenal failure	Glomerular filtration rate abnormal	Glomerular filtration rate abnormal
	Renal failure acute	Glomerular filtration rate decreased	Glomerular filtration rate decreased
	Renal injury	Haemodialysis	GRACILE syndrome
	Renal ischaemia	Haemofiltration	Haemodialysis
	Renal tubular injury	Hypercreatininaemia	Haemofiltration
	Renal tubular necrosis	Intradialytic parenteral nutrition	Haemolytic uremic syndrome
	Traumatic anuria	Neonatal anuria	Hepatorenal failure
	Tubulointerstitial nephritis	Nephritis	Hypercreatinaemia
	Urate nephropathy	Nephropathy toxic	Hypercreatininaemia
	Urine output decreased	Oedema due to renal disease	Malignant urinary tract obstruction
		Oliguria	Metabolic nephropathy
		Peritoneal dialysis	Nephritis
		Prerenal failure	Nephropathy toxic
		Protein urine present	Oedema due to renal disease
		Proteinuria	Oliguria
		Renal failure	Pancreatorenal syndrome
		Renal failure neonatal	Postoperative renal failure
		Renal function test abnormal	Postrenal failure
		Renal impairment	Prerenal failure
		Renal impairment neonatal	Renal disorder
		Renal transplant	Renal failure
		Renal tubular disorder	Renal failure acute
		Renal tubular necrosis	Renal function test abnormal
		Tubulointerstitial nephritis	Renal impairment
		Urea renal clearance decreased	Renal injury
		Urine output decreased	Renal insufficiency
			Renal ischaemia
			Renal procedural complication
			Renal tubular disorder
			Renal tubular dysfunction
			Renal tubular injury
			Renal tubular necrosis
			Subacute kidney injury
			Traumatic anuria
			Tubulointerstitial nephritis

ARF SMQ N (MedDRA v. 18.1)	AKI FMQ N (FMQ v. 2.1)	ARF SMQ B (MedDRA v. 18.1)	AKI FMQ B (FMQ v. 2.1)
			Urate nephropathy
			Urea renal clearance decreased
			Urinary tract toxicity
			Urine output decreased

Nausea FMQ N (FMQ v. 2.0)	Vomiting FMQ N (FMQ v. 2.0)	Diarrhea FMQ N (FMQ v. 2.0)
Nausea	Acetonaemic vomiting	Allergic gastroenteritis
Nausea aggravated	Cyclic vomiting syndrome	Amoebic dysentery
Nausea post chemotherapy	Discoloured vomit	Antidiarrheal supportive care
Nausea postoperative	Epidemic vomiting syndrome	Antidiarrhoeal supportive care
Post procedural nausea	Faecal vomiting	Autoimmune enteropathy
Procedural nausea	Haematemesis	Bacterial diarrhoea
	Hyperemesis gravidarum	Cholera
	Infantile vomiting	Diarrhoea
	Post procedural vomiting	Diarrhoea aggravated
	Post-tussive vomiting	Diarrhoea haemorrhagic
	Procedural vomiting	Diarrhoea infectious
	Regurgitation	Diarrhoea neonatal
	Regurgitation of food	Diarrhoea NOS
	Self-induced vomiting	Diarrhoea postoperative
	Vomiting	Dysentery
	Vomiting aggravated	
	Vomiting in pregnancy	
	Vomiting neonatal	
	Vomiting NOS	
	Vomiting of medication	
	Vomiting postoperative	
	Vomiting projectile	
	Vomiting psychogenic	

Source: FMQ v. 2.0 (see www.regulations.gov/docket/FDA-2022-N-1961/document); SMQ v. 18.1 (see www.meddra.org/standardised-meddra-queries).
Abbreviations: FMQ, FDA medical query; MedDRA, Medical Dictionary for Regulatory Activities; NOS, not otherwise specified; SMQ, standardized Medical Dictionary for Regulatory Activities query

Table 30. Synopses of Case Narratives for Serious AKI Events in the ITCA 650 Clinical Development Program

Subject	Baseline eGFR*	Dosing Regimen	Study Day	Synopsis
AKI 1 (CLP-105)	79	ITCA 650 20 mcg	39	54 yo male with nausea, vomiting, and diarrhea, admitted to hospital for AKI and gastroenteritis (no Cr available). Discharged after 4 days, then returned 1 week later with Cr 4.9**. Discharged after 4 days with Cr 1.2. Device was not removed, subject remained in the study and renal function recovered to baseline.
AKI 2 (CLP-107)	58	ITCA 650 60 mcg	502 (46 days after device replacement)	66 yo female taking warfarin who underwent bilateral lower extremity venous cauterization for venous insufficiency. The subject had excessive bleeding from varicose vein requiring transfusion, found to have supratherapeutic INR (>10) and AKI with Cr 2.6 recovered to 0.8. Subject remained in study.
AKI 3 (CLP-107)	63	ITCA 650 20 mcg	7	76 yo male with baseline Cr 1.0 who had endoscopy for Barrett's esophagus 2 days after initial device placement, followed by new-onset watery diarrhea and vomiting. Subject admitted with hypotension and AKI (Cr 3.8). Recovered with treatment including IVF and discharged after 3 days. Subject remained in study.

Subject	Baseline eGFR*	Dosing Regimen	Study Day	Synopsis
AKI 4 (CLP-107)	62	ITCA 650 60 mcg	117 (30 days after first 60 mcg device placed)	74 yo male with baseline Cr 1.1, who presented after dose escalation to 60 mcg/day device with nephrolithiasis, hypertension, and chest pain; Cr 1.5. Subject improved, but was readmitted 1 week later with severe diarrhea, dehydration, and AKI (Cr 2.3). AKI resolved with treatment; device removed 4 days into hospitalization due to ongoing diarrhea and subject discontinued from study.
AKI 5 (CLP-107)	57	ITCA 650 20 mcg	75	68 yo female with baseline Cr 1.0 who developed nausea, vomiting, and diarrhea approximately 2 months after initial device placement, admitted with dehydration (+orthostatic hypotension), urinary tract infection, and AKI (Cr 1.8). Treated with intravenous fluids and antibiotics and discharged. On Study Day 92, subject underwent placement of the ITCA 60 mcg/day device; over the subsequent 3 months Cr remained elevated (1.5-2.1) and nephrology consult was obtained. Device removed on Study Day 183 and subject recovered; on Study Day 195 Cr was 1.0; on Study Day 225 Cr was 0.87.
AKI 6 (CLP-107)	68	ITCA 650 20 mcg	19	67 yo male with baseline Cr 1.1-1.3, who presented 17 days after initial device placement with nausea, vomiting, and abdominal pain, elevated pancreatic enzymes, and AKI (Cr 3.6). ITCA 650 device was removed during hospitalization, subject was treated with intravenous fluids and Cr returned to baseline.
AKI 7 (CLP-107)	50	ITCA 650 60 mcg	748 (109 days after device replacement)	73 yo male with baseline Cr 1.3, noted to have nausea and vomiting from Study Day 609-747. Hospitalized by primary care physician on Study Day 748 for nausea, vomiting, dehydration, ketonuria, and AKI (Cr not reported). Discharged after 1 day, then represented 2 days later with nausea, vomiting, dehydration, gastritis, duodenitis, hematemesis (Cr not reported). On admission noted to have intractable nausea/vomiting, anorexia, hyponatremia, weakness, confusion, AKI and fever. Improved with treatment and Cr on discharge was 1.1. Device removed 2 days after discharge.
AKI 8 (CLP-107)	64	ITCA 650 60 mcg	266 (1 day after device replacement)	75 yo female with baseline Cr 0.7-0.9, who underwent second device replacement on Study Day 269, and on the same day was diagnosed with UTI and AKI (no Cr reported in original narrative). Treated with ciprofloxacin and developed diarrhea, vomiting, fatigue and abdominal/low back pain 8 days later for which she took naproxen. On Study Day 281 subject was hospitalized with Cr 3.0; AKI resolved with treatment (Cr 1.1 at discharge). Subject remained in the study.
AKI 9 (CLP-107)	80	ITCA 650 60 mcg	312 (44 days after device removal)	65 yo male w/ baseline Cr 1.0, admitted 44 days after final ITCA 650 device removal with severe dehydration (no Cr available). Received IVF and discharged 2 days later. Subject lost to follow-up and no further records obtained.

Subject	Baseline eGFR*	Dosing Regimen	Study Day	Synopsis
AKI 10 (CLP-107)	48	ITCA 650 60 mcg	111 (17 days after 60 mcg device placed)	43 yo male w/ baseline Cr 1.3 who had nausea and vomiting from Study Days 4 through 18 after placement of the ITCA 20 mcg/day device. Underwent placement of the ITCA 60 mcg/day device on Study Day 94 and had nausea and vomiting starting on Study Day 107 admitted for dehydration and AKI (Cr 2.6). Diagnosed with gallstones during admission. Recovered with treatment. Subject remained in study. Cr 1.6 on Study Day 312.
AKI 11 (CLP-107)	52	ITCA 650 20 mcg	0	63 yo male w/ baseline Cr 1.2, noted to have AKI (Cr 1.4) on labs obtained prior to device placement. Saw nephrologist and stopped spironolactone on Study Day 4; on Study Day 7 subject was hospitalized for worsening AKI (Cr 1.8), diagnosed with diabetic glomerulosclerosis. Subject remained in the study and had subsequent hospitalizations for heart failure.
AKI 12 (CLP-107)	83	ITCA 650 60 mcg	559 (101 days after device replacement)	64 yo female with baseline Cr 0.7 who presented with several days of vomiting, diarrhea, abdominal pain, and an episode of syncope the morning of hospitalization, found to have AKI (Cr 9.3). Required two rounds of dialysis, then recovered to baseline renal function (Cr on Study Day 701 was 0.7). Subject remained in the study.
AKI 13 (CLP-107)	62	ITCA 650 20 mcg	8	73 yo male with baseline Cr 1.1 who developed nausea, vomiting, and diarrhea on Study Day 5, diagnosed with UTI on Study Day 7 and prescribed cefuroxime and diclofenac; became anuric and admitted for ARF (Cr 3.0) on Study Day 8. Recovered with treatment; Cr was 1.2 on Study Day 462. Subject remained in study.
AKI 14 (CLP-107)	87	ITCA 650 20 mcg	8	61 yo male with baseline Cr 0.9 who developed nausea, vomiting, anorexia and dizziness the day after initial device placement, hospitalized for AKI (Cr 4.3). Study device was removed 2 days into hospitalization and subject improved and was discharged 2 days later. Subject discontinued from the study. Last available Cr 1.1 on Study Day 549.
AKI 15 (CLP-107)	87	Placebo	460 (185 days after device replacement)	66 yo male with mild renal impairment at baseline, who presented with fever and vomiting, found to be in hyperglycemic hyperosmolar acidosis secondary to poorly controlled diabetes and UTI (glucose 621, A1C 15, AG 25; glucose peaked at 900; the subject was in renal failure with Cr 2.5). This subject developed septic shock and ultimately expired due to complications related to septic shock.
AKI 16 (CLP-107)	80	Placebo	632 (0 days after device replacement)	61 yo female w/ baseline Cr 0.8 who developed diarrhea 13 days prior to her device removal/replacement procedure. On the day of the procedure, creatinine was found to be 1.9 mg/dL. The event resolved with temporary discontinuation of metformin and oral hydration–the narrative does not mention hospitalization. Cr returned to 1.0 at 10 days after the event started. This ARF event was coded as an SAE because it was checked as “medically significant” in the narrative form.

Subject	Baseline eGFR*	Dosing Regimen	Study Day	Synopsis
AKI 17 (CLP-107)	55	Placebo	168 (77 days after device replacement)	71 yo male w/ baseline moderate renal impairment, hospitalized worsening of ischemic heart disease and received coronary angiogram approximately 2 months after his first device removal/replacement. Based on results, the subject was scheduled for CABG but the operation was cancelled because the subject developed anuric AKI 2 days after angiogram. He was admitted 5 days after angiogram with Cr of 8 mg/dL and hospitalized for 10 days until renal function recovered. Approximately 1 month later, the subject died at home of unknown causes.
AKI 18 (CLP-107)	65	Placebo	107 (15 days after device replacement)	70 yo female presented to ER 10 days after device removal/replacement procedure for a furuncle in the inguinal region given Augmentin. Two days later, she developed watery diarrhea, vomiting, and abdominal cramping. Two days after that, she returned to the ER with symptoms of dehydration (decreased urine output, dizziness, diarrhea and vomiting) and was admitted with AKI with creatinine 8.7 and potassium 7.1. She received hemodialysis for several days, recovered renal function and was discharged.

Source: CDER Reviewer's summary of narratives submitted to SDN 0000 and SDN 0059; data: adsl.xpt and adae.xpt from SDN0000

* eGFR is presented in mL/min/1.73m^2

** Cr is presented in units of mg/dL throughout case synopses.

Abbreviations: AKI, acute kidney injury; ARF, acute renal failure; CABG, coronary artery bypass graft; Cr, creatinine; ER, emergency room; A1C, hemoglobin A1C; INR, international normalized ratio; ITCA 650, exenatide in DUROS device; IVF, intravenous fluids; UTI, urinary tract infection; yo, years old

Table 31. Time to First Occurrence of 3-Point MACE (CV Death, Nonfatal MI, Nonfatal Stroke) and 4-Point MACE (CV Death, Nonfatal MI, Nonfatal Stroke, Unstable Angina) – ITT Population End of Treatment, Pooled Analysis of CLP-103, CLP-105, and CLP-107

Mace Type	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	73/2641 (2.8%) [2.54]	61/2493 (2.4%) [2.11]	1.24 (0.88, 1.74)
4-Point MACE	83/2641 (3.1%) [2.9]	71/2493 (2.8%) [2.5]	1.20 (0.87, 1.66)

Source: Tables 15 and 16 of the CDER Safety Statistics Review (DARRTS August 11, 2017).

One hundred sixty positively adjudicated 3-point MACE events (154 in FREEDOM, 6 in glycemic control trials).

** Hazard ratios were estimated based upon a Cox model stratified by CV risk group and Study with a fixed effect for treatment.

Abbreviations: CI, confidence interval; CV, cardiovascular; DARRTS, Document Archiving, Reporting, and Regulatory Tracking System; HR, hazard ratio; IR, incidence rate per 100 patient-years; ITCA 650, exenatide in DUROS device; MACE, major adverse cardiovascular event; MI, myocardial infarction; PY, patient-years

Table 32. Time to First Occurrence of 3-Point MACE (CV Death, Nonfatal MI, Nonfatal Stroke) and 4-Point MACE (CV Death, Nonfatal MI, Nonfatal Stroke, Unstable Angina) – ITT Population End of Treatment +30 Days, FREEDOM (CLP-107)

Mace Type	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*	77/2070 (3.7%) [3.0]	61/2074 (2.9%) [2.3]	1.31 (0.94-1.83)
4-Point MACE	85/2070 (4.1%) [3.3]	71/2074 (3.4%) [2.6]	1.24 (0.91-1.70)

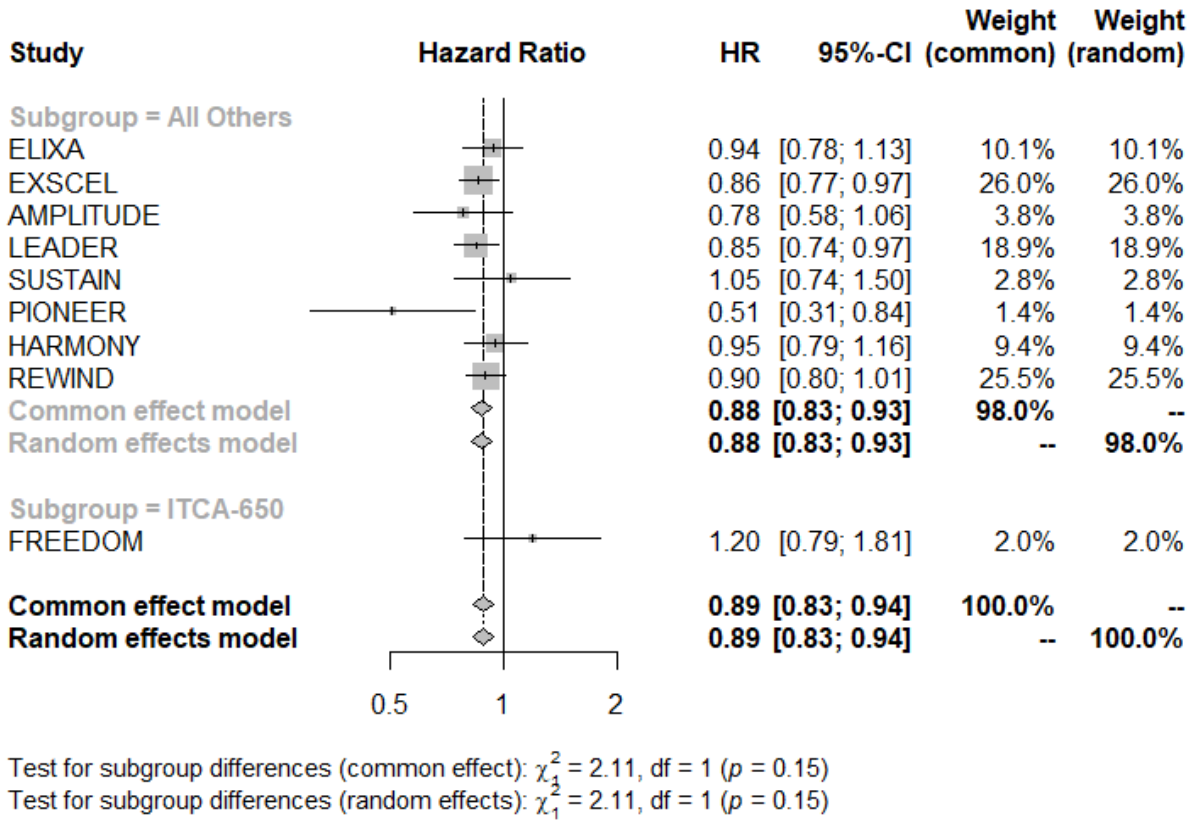
Source: CDER Review staff. Analysis: R v. 4.2 (MACE.R); data: adef.xpt from SDN0000.

* One hundred fifty-four positively adjudicated 3-point MACE events in FREEDOM.

** Hazard ratios were estimated based on a Cox model stratified by CV risk group with a fixed effect for treatment.

Abbreviations: CI, confidence interval; CV, cardiovascular; DARRTS, Document Archiving, Reporting, and Regulatory Tracking System; HR, hazard ratio; IR, incidence rate per 100 patient-years; ITCA 650, exenatide in DUROS device; MACE, major adverse cardiovascular event; MI, myocardial infarction; PY, patient-years

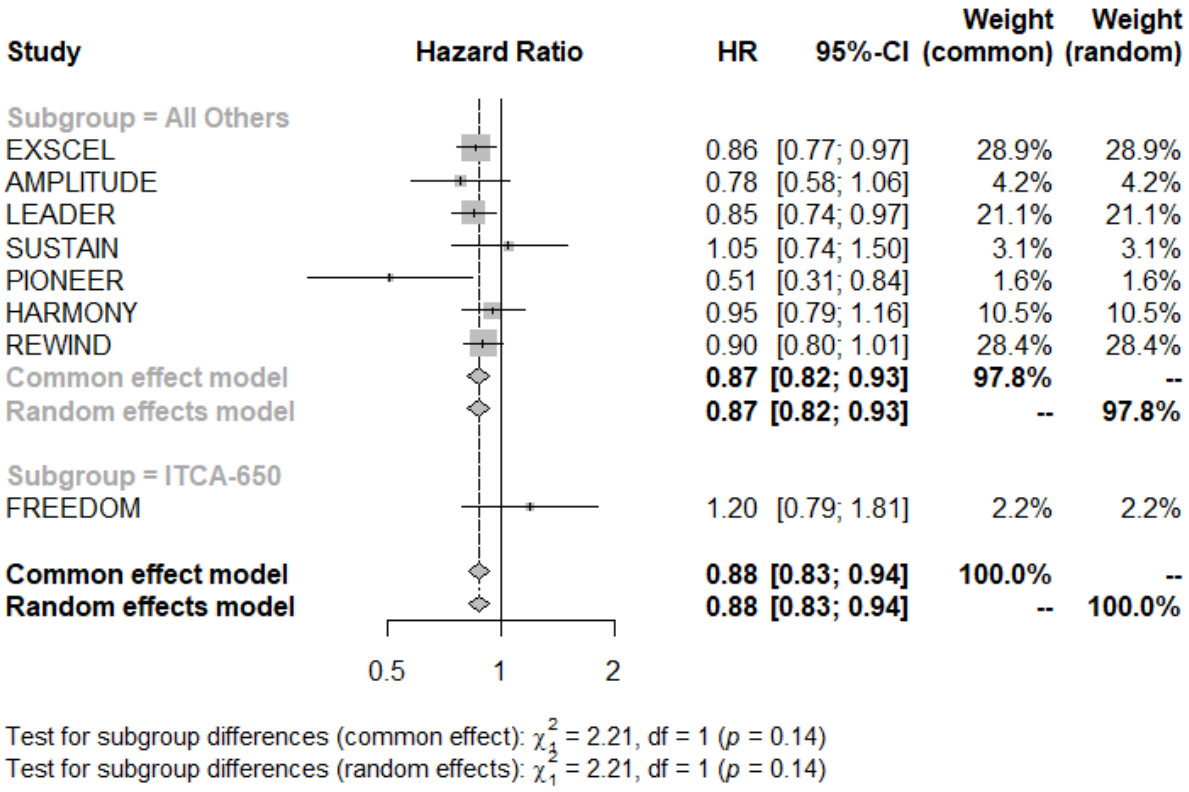
Figure 22. Meta-Analysis of All-Cause Mortality Across CVOTs in the GLP1RA Class



Source: CDER Review staff. R v. 4.3, using the R package 'meta' (Balduzzi et al. 2019); data derived from Table 22.

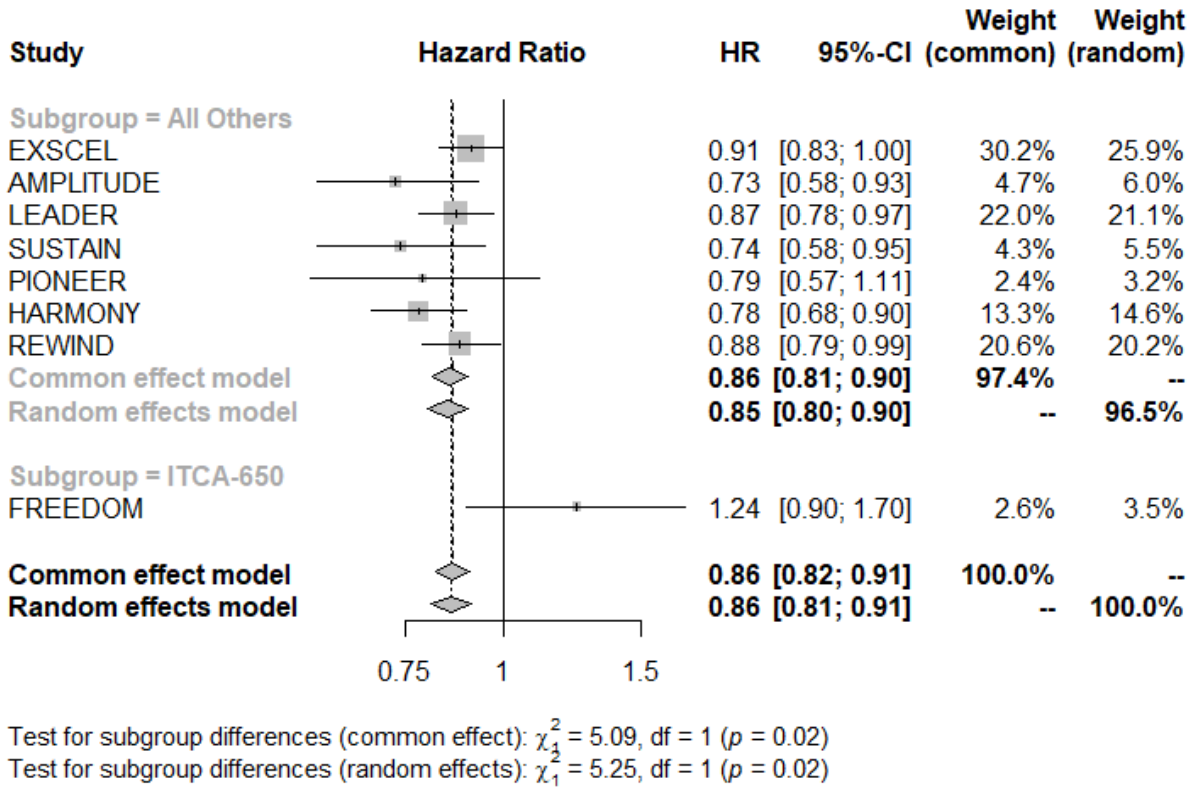
Abbreviations: CI, confidence interval; EOS, end of study; GLP1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; ITCA 650, exenatide in DUROS device MACE, major adverse cardiovascular event

Figure 23. Meta-Analysis of All-Cause Mortality Across CVOTs in the GLP1RA Class (FDA Analysis, ELIXA Excluded)



Source: CDER Review staff. R v. 4.3, using the R package 'meta' (Balduzzi et al. 2019); data derived from Table 22.
Abbreviations: CI, confidence interval; EOS, end of study; GLP1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; ITCA 650, exenatide in DUROS device MACE, major adverse cardiovascular event

Figure 24. Meta-Analysis of 3-Point MACE Across CVOTs in the GLP1RA Class (ELIXA Excluded)



Source: CDER Review staff. R v. 4.3, using the R Package 'meta' (Balduzzi et al. 2019); data derived from Table 22.
Abbreviations: CI, confidence interval; CVOT, cardiovascular outcomes trial; EOS, end of study; GLP1RA, glucagon-like peptide-1 receptor agonist; HR, hazard ratio; ITCA 650, exenatide in DUROS device MACE, major adverse cardiovascular event

Table 33. Time to First Occurrence All Serious Adverse Events – mITT Population End of Treatment +30 Days, FREEDOM (CLP-107)

Parameter	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. Analysis: R v. 4.2 (MACE.R); data: adef.xpt from SDN0000.
Abbreviations: CI, confidence interval; HR, hazard ratio; IR, incidence rate per 100 patient-years; ITCA 650, exenatide in DUROS device; PY, patient-years

5.3 Detailed Regulatory History

Table 34. Key Meetings and Regulatory Interactions for NDA 209053 (IND 102105)

Date	Meeting/Submission Type	Comments
Sep 9, 2010	EOP2 meeting FDA preliminary comments issued	• CDER provided advice on the design of the Phase 3 program, design of the cardiovascular outcome trial, and observations from the Phase 2 and in vitro data that would require justification in the NDA submission.[1] • In response to CDER's comments, the Applicant cancelled the scheduled EOP2 meeting to review and revise their Phase 3 program.
Dec 16, 2010	Revised EOP2 meeting package submitted	• Phase 3 Study CLP-03 draft protocol included plans for extensive pharmacokinetic assessments throughout the trial from Day 0 out to Week 52.[2]
Jan 18, 2011	EOP2 meeting (meeting minutes issued Feb 11, 2011)	• Topics discussed included elements required for a 505(b)(1) versus 505(b)(2) NDA submission and the Applicant's plan for their CV risk assessment to satisfy the December 2008 CV guidance.[3]
Jun 18, 2012	Study CLP-107 (CVOT) protocol submitted	• The Applicant's submission outlined their initial proposals for their CVOT design.[4]
Aug 31, 2012	Advice Letter with CDER comments on Study CLP-107 protocol	• CDER provided advice on the Applicant's CVOT design and statistical comments on the censoring schemes that should be submitted to evaluate CV risk.[5]
Nov 30, 2012	Study CLP-103 (formerly CLP-03) protocol amendment submitted	• The Applicant removed the provisions for collection of pharmacokinetic assessments during the trial.[6]
Apr 19, 2013	Advice Letter with CDER comments on revised protocol Study CLP-107	• CDER provided additional statistical advice regarding the design and analyses of the proposed CVOT.[7]
May 23, 2014	Applicant submitted revised protocol Study CLP-107	• The Applicant submitted justification for their proposal to assume a HR below 1 for the MACE-3 endpoint for ITCA 650 vs. placebo.[8]
Jul 17, 2014	Advice Letter with CDER comments on revised protocol Study CLP-107	• CDER disagreed with the Applicant's justification for assuming a true HR for MACE-3 below 1.0.[9]
Jan 9, 2015	Advice Letter on Study CLP-103 and CLP-103 substudy protocols	• CDER provided advice on study design and analyses, including handling of missing data.[10]
Aug 26, 2015	Advice Letter on Study CLP-105 protocol	• CDER provided advice on minimizing and handling of missing data.[11]
Aug 30, 2016	Type B pre-NDA meeting (meeting minutes issued Sep 29, 2016)	• Topics discussed included the planned time-to-event CV analyses for the CVOT.[12]
Nov 21, 2016	NDA 209053 submission	• PDUFA goal date Sep 21, 2017.
Sep 18, 2017	Applicant communication to CDER	• The Applicant notified CDER of unexpected **out-of-specification results for sterility** during routine testing: *Bacillus pumus* and *Bacillus paralichiformus* were identified in two ITCA product lots.

Date	Meeting/Submission Type	Comments
Sep 21, 2017	NDA 209053 Complete Response Letter issued IND 102105 placed on Full Clinical Hold	• Major clinical deficiencies included imbalances in AKI and serious AKI events unfavorable to ITCA 650, a finding that was not observed in other GLP1RA development programs, and a nonreassuring cardiovascular risk meta-analysis, especially in older patients and patients with chronic kidney disease. • Other major deficiencies included failure to demonstrate consistent release of drug product from the device and product quality deficiencies. Major cGMP deficiencies were observed in manufacturing site inspections. • Due to sterility testing results demonstrating two lots of ITCA 650 were not sterile, the IND was placed on Full Clinical Hold and all ongoing clinical studies were halted. • The IND remains on Full Clinical Hold to this date.
May 8, 2018	Type B End-of-Review Meeting Minutes (meeting minutes issued Jun 8, 2018)	• Topics discussed included the need for device verification based on the clinically relevant design requirement, which is daily exenatide dose.[13]
Sep 9, 2019	NDA 209053 resubmission	• PDUFA goal date Mar 9, 2020
Mar 9, 2020	Complete Response Letter issued	• As a path forward CDER recommended: "To address the clinical deficiencies, you should address all the major device and product quality related deficiencies below and provide additional clinical data that adequately address the above clinical risks and establish that ITCA 650 is safe and effective for the intended use. Based on the findings of the device review and the product quality review, we recommend that you redesign the product such that it provides reliable and clinically appropriate exenatide release rates over the life of the product and that you conduct new clinical trials to demonstrate the efficacy and safety of the redesigned drug-device combination product."
Jun 5, 2020	FDDR submitted	• FDRR to OCHEN level.
Jul 30, 2020	Appeal Denied letter issued	• Dr. Ellis Unger (former Director, OCHEN) issued the letter.[14]
Aug 14, 2020	FDDR submitted	• FDRR to OND level.
Oct 30, 2020	Appeal Denied letter issued	• Dr. Robert Temple (Senior Advisor, OND) issued the letter.[15]
Nov 27, 2020	FDDR submitted	• FDRR to CDER level. • Formal Dispute meeting between CDER and the Applicant occurred on Jan 15, 2021. • The Applicant requested an Advisory Committee meeting for the first time during the Center-level dispute process.
Feb 12, 2021	Appeal Denied letter issued	• Dr. Douglas Throckmorton (Deputy Director for Regulatory Programs, Office of the Center Director, CDER) issued the letter.[16]

Date	Meeting/Submission Type	Comments
Mar 16, 2021 to Oct 10, 2022	The Applicant submitted a request under 21 CFR 314.110(b)(3) for an opportunity for a hearing on whether there are grounds under section 505(d) of the FD&C Act for denying approval of NDA 209053 (Mar 16, 2021)	• CDER published a NOOH regarding CDER's proposal to refuse to approve NDA 209053 in the Federal Register on Sep 2, 2021. • The NOOH gave the Applicant an opportunity to request a hearing before the Commissioner of Food and Drugs on CDER's proposal to refuse to approve NDA 209053. • The Applicant submitted a notice of participation and request for a hearing on Sep 13, 2021, followed by information and analyses in support of its hearing request on Nov 1, 2021, and Feb 15, 2022. • CDER served the Applicant with a proposed order denying the Applicant's hearing request on Jul 29, 2022. • The Applicant submitted a response to CDER's proposed order denying the Applicant's hearing request on Oct 10, 2022.
Feb 7, 2023 to Mar 24, 2023	Chief Scientist issued a letter to the Applicant, and to CDER (Feb 7, 2023)	• The letter invited the Applicant to request a public hearing before an advisory committee under 21 CFR part 14 in lieu of a formal evidentiary hearing under 21 CFR part 12. • The Applicant submitted a request for a public hearing before an advisory committee under 21 CFR part 14 on Feb 20, 2023. • The Chief Scientist granted the Applicant's request for a public hearing before an advisory committee under 21 CFR part 14 on Mar 24, 2023.

Source: CDER Reviewer's summary.

[1] CDER provided the following key advice in the preliminary comments:

- A single pivotal Phase 3 trial would be inadequate to support an NDA submission.
- The Phase 3 program would need to adequately address safety concerns specific to ITCA 650, including higher exenatide PK exposures than those observed with Byetta.
- CDER noted the high incidence of persistent nausea (≥20%) at the 60 mcg dose in the Phase 2 program, and recommended exploring a 20 mcg/40 mcg dosing regimen as well as an option for 20 mcg maintenance therapy with up-titration if needed for glycemic control.
- CDER stated the NDA submission should contain justification for the wide range of drug release rates from the device presented in the Applicant's meeting package.
- CDER stated the Applicant would be required to conduct a cardiovascular outcomes study with ITCA 650 designed to meet the noninferiority margin described in the guidance for industry, *Diabetes Mellitus—Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes* (December 2008).
- CDER disagreed with the Applicant's proposal to exclude patients with clinically significant cardiovascular disease from their Phase 3 program.

[2] Phase 3 Study CLP-03 draft protocol included the following statements regarding planned pharmacokinetic assessments:

- "PHARMACOKINETICS: Plasma exenatide concentration will be measured at Day 0, Weeks 1, 6, 13, 14, 20, 26, 27, 39 and 52" (page 5-13).
- "PK analysis will include a set of summary statistics describing the serum exenatide concentration at each timepoint for which data are available" (page 5-14).
- "Pharmacokinetics: Blood samples for PK assessment will be collected at all visits except Screening Visit 1 and 2 and Visit 13 (ET + 4 weeks). Blood samples for PK assessment will be collected prior to any insertion and/or removal procedure being performed" (Section 5.2.2, page 5-43).
- "PHARMACOKINETIC ASSESSMENTS: Specification of Variables and Procedures: The concentration of exenatide will be measured. Other PK parameters may be calculated as appropriate" (Section 9, page 5-53).
- PK timepoints were presented in, Trial Procedures, under the description of assessments for each study visit (Section 5, page 5-33 to 5-41).
- "Pharmacokinetic Analysis: Pharmacokinetic analyses will include a set of summary statistics describing the serum exenatide concentration at each time point for which data are available" (Statistics, Section 12.7.3, page 5-68).
- Appendix A: Schedule of Procedures; PK timepoints from the text were presented in tabular format with a footnote stating: "PK samples should be collected prior to removal of ITCA 650 or ITCA placebo" (page 5-77).

[3] CDER provided the following key advice:

- CDER advised the Applicant that they should submit a proposal clarifying how they intended to satisfy the guidance (December 2008) to demonstrate ITCA 650 is not associated with an unacceptable increase in cardiovascular risk.
- Discussion occurred regarding whether the Applicant would pursue the 505(b)(2) pathway with Byetta or exenatide once-weekly (i.e., Bydureon, which was not yet approved at the time of the meeting) as the listed drug versus a 505(b)(1) pathway. CDER was unable to comment on the proposal to rely in part on Bydureon to satisfy aspects of the ITCA 650 program because it was not yet approved but noted that the listed drug relied upon for approval of ITCA 650 could be changed up until submission of the NDA.

- CDER stated that the Applicant's proposed clinical program, addressing the comments in the meeting comments including those related to the CV risk assessment, would be adequate to support a 505(b)(1) NDA provided that no unexpected findings were to arise in the development program.

[4] The Applicant's key initial proposals for the CVOT were:

- To define MACE as the composite endpoint of CV death, nonfatal MI, nonfatal stroke, and hospitalization for unstable angina, i.e., 4-point MACE.
- The proposed primary hypothesis was to show the HR of MACE for ITCA 650 versus placebo was <1.8; under the Applicant's proposal data would not be available at the time of the NDA submission to demonstrate an NI margin <1.8. The proposed secondary hypothesis was to show the HR of MACE for ITCA 650 vs placebo was <1.3.
- The Applicant proposed to provide a postapproval meta-analysis of Study CLP-107 with the Phase 3 studies to demonstrate an NI margin <1.3.
- The Applicant stated that if the observed HR in their interim analysis is <1 (i.e., favorable to ITCA 650), a relatively small number of MACE events would be needed to demonstrate the NI criteria are met with >90% power. The Applicant provided an example power calculation in their meta-analysis plan assuming a true HR of 0.8.

[5] CDER provided the following key advice:

- To satisfy the requirements of the 2008 guidance, the Applicant must rule out a CV risk margin of 1.8 premarketing.
- It may be acceptable to combine data in a meta-analysis from the Phase 3 safety and efficacy trials to accumulate the necessary data to rule out the required premarketing 1.8 NI margin.
- To rule out the postmarketing NI margin of 1.3, CDER encouraged using only data from trials that have sufficiently long exposure and are conducted in relevant populations for which CV safety risk is of the greatest concern (i.e., populations enriched with subjects at high risk for CV events); and stated that typically such data are derived from event-driven CV safety trials, not a meta-analysis that includes trials that are not designed around a CV primary endpoint.
- CDER recommended redesigning Study CLP-107 to plan for sufficient events to rule out the 1.3 margin with 90% power without combining data from other studies in a meta-analysis.
- CDER stated: "You should meet the 1.3 noninferiority margin from a dedicated CV outcomes trial. While it cannot be definitively determined that additional CV safety data would not be needed, meeting the postmarketing risk margin of 1.3 is acceptable."
- CDER stated that absent empirical data, the Applicant should not design their development program around an assumption that the true CV HR is below 1.
- CDER stated the following regarding CV safety analyses: "For analyses of cardiovascular safety, the Agency has taken the stance of requiring three separate censoring schemes for the primary analyses. The first is censoring all subjects at time of first event, dropout, or end of treatment. The second censoring scheme censors subjects at time of first event, dropout, or 30 days after the end of treatment. The final censoring scheme censors subjects at time of first event, dropout, or the end of the study. Primary and major secondary analyses (e.g., MACE components) should be carried out using all three censoring schemes. On-study/intent-to-treat exposure may be treated as the primary population."

[6] Removal of PK assessments was not included in the text summary of protocol changes introduced by the statement, "In ITCA 650-CLP-103, please note the following differences from ITCA 650-CLP-03:" (Section 2, page 2-3). Removal of PK assessments was not included in the table titled "Summary of Changes" (pages 5-100 to 5-107), which described other changes made to the protocol, the affected sections and associated text, and the rationale for each change. Pharmacokinetic assessment information was removed from the protocol synopsis, protocol text, the descriptions of Trial Procedures for each study visit, the description of planned statistical analyses, and Appendix A: Schedule of Procedures (page 5-177 of submission).

[7] CDER noted that the Applicant's evaluation of the primary composite 4-point MACE endpoint was based on an assumption that the true HR is 1.0, but that the evaluation of the 3-point MACE endpoint (i.e., CV death, nonfatal MI, nonfatal stroke) was based on an assumption that the true HR is 0.8, reflecting superiority of ITCA 650 to placebo. The Agency reiterated that the Applicant had not submitted sufficient justification to assume a true HR below 1.0.

[8] To support this assumption, the Applicant cited pooled analyses of 3-point MACE in the exenatide and liraglutide Phase 3 glycemic control development programs.

[9] CDER noted that the pooled analyses of exenatide and liraglutide cited by the Applicant were based on less than one year of exposure and collected a limited number of events (less than 50 in each analysis) reflected in wide 95% CIs. CDER stated the HR point estimates were therefore unstable and should not be relied on to estimate power for Study CLP-107. CDER reiterated its recommendation that the Applicant power the study assuming a HR=1 for both the premarket and postmarket CV requirements, and that the study be powered at 90%.

[10] CDER provided the following key advice:

- The Applicant planned to define the primary analysis set as the modified intention-to-treat population consisting of all randomized subjects who receive at least one treatment of ITCA 650 or placebo and have a valid baseline and at least one postbaseline A1C measurement. CDER stated that to follow the intention-to-treat principle, the Applicant should include all randomized subjects in the analysis.
- CDER stated that the Applicant should specify a primary analysis that does not rely on the Last Observation Carried Forward (LOCF) approach to handling missing data.
- CDER stated that a sizable amount of missing data will impact our confidence in study findings.

[11] CDER provided the following key advice:

- CDER noted 20.4% premature study withdrawal rate from Study CLP-103, mostly due to withdrawal by the subject or AEs, and that substantial missing data will impact our confidence in the study findings.
- CDER recommended that subjects who discontinue study treatment should continue to be followed for A1C measurement and other key endpoints.
- CDER did not agree with the Applicant's approach to consider post-rescue data as missing. CDER recommended use of the ITT estimand and noted evaluation of the ITT estimand will be critical from a regulatory perspective.

[12] The following points were discussed:

- CDER stated the time-to-CV event analysis dataset should contain information relevant for the planned time-to-event analyses; e.g., subject and trial identification, demographics, risk factors, treatment group, population flags, cardiovascular composite endpoint(s), individual components, censoring flag, censoring date and event date. All composite endpoints specified in the meta-analysis protocol (e.g., primary and secondary MACE endpoints), and respective components, as well as all-cause mortality, should be accounted for in this dataset. The dataset should also contain any variable relevant for protocol-specified subgroup CV analyses.
- The Applicant clarified that the meta-analysis of MACE was the primary endpoint of Study CLP-107 but that a full analysis of the CLP-107 study population was conducted for all primary and secondary endpoints and overall safety and would be included in the CLP-107 Clinical Study Report.

[13] The following points were discussed:

- The Applicant stated their position that weekly/biweekly testing intervals are the appropriate basis for the IVR specifications.
- CDER stated that weekly or biweekly device output measurements may be appropriate for lot release as a quality control strategy, but are not appropriate for device design verification and validation. CDER stated that the device should be verified and validated against a clinically relevant design requirement, i.e., daily dosing of exenatide. CDER noted that the recommended dosing of the product is described as mcg/day and therefore the design requirement for the device should be aligned with this intended use, and that daily release rate should be characterized as part of design verification and validation if the intended labeling is for daily dosing of the drug.
- CDER stated that there were instances of early device depletion indicating the device delivered at a rapid rate or had intermittent instances of dose dumping and that weekly and biweekly measurements did not show consistent day to day performance for the entirety of the implant duration.
- CDER recommended that that Applicant propose a new test plan that verifies the clinically relevant specification (i.e., daily sampling); CDER noted the burden of daily testing for 6 months and stated willingness to review alternative plans that ensure consistent delivery at the daily sampling rate throughout the duration of the implant.

[14] Dr. Unger's FDRR Appeal Denied letter stated:

- "I agree with the Division's conclusion: there is an imbalance in AKI events in the ITCA 650 FREEDOM CVOT, but no imbalances in AKI in the CVOTs for liraglutide (LEADER) or semaglutide (SUSTAIN-6)."
- The letter noted the concerning HR for MACE in FREEDOM (the ITCA 650 CVOT), the additional concerning MACE analyses in subjects ≥65 years of age and with baseline renal impairment, and the deficiencies identified in the device review.
- As a possible path forward, Dr. Unger stated: "I agree with the Division that to address the deficiencies, you should address all the major device- and product quality-related deficiencies in the CR letter and provide additional clinical data that adequately address the clinical risks, to establish that ITCA 650 is safe for its intended use. You will need to show that the product provides reliable and clinically appropriate exenatide release rates over the life of the product. You may consider demonstrating additional benefits that would outweigh the serious risk of AKI (e.g., evidence of improved microvascular disease risk reduction versus available exenatide therapies) and/or demonstrating, in new clinical studies, that the risk of AKI can be sufficiently mitigated such that the benefit-risk profile becomes favorable."

[15] Dr. Temple's FDRR Appeal Denied letter stated:

- "The imbalance in AKI events seen with ITCA 650, which appears to persist over time, has not been observed in the cardiovascular outcomes trials of any of the other GLP1RA drugs and remains a valid reason for issuing the Complete Response letter."
- The letter stated: "I am also highly concerned with the MACE results of the FREEDOM Trial which, as Dr. Unger noted, essentially rule out the beneficial effect seen in the EXSCEL Trial of Bydureon (exenatide extended release). Indeed, the results of the FREEDOM Trial suggest a possible adverse effect of ITCA 650 on MACE events."
- "Intarcia will need to address all of the deficiencies cited in the CR letter, in Dr. Unger's appeal response, and in my analysis above."

[16] Dr. Throckmorton's FDRR Appeal Denied letter stated:

- "…there are foundational scientific issues that FDA staff have identified that would not benefit from an AC discussion at this time. Instead, I recommend that you formulate a plan to address the issues identified in the March 9, 2020, Complete Response letter."
- "…generating additional clinical data that address the AKI and cardiovascular safety signals is necessary, for example, conducting a new pre-market CVOT."
- "Given the findings from CDRH, I recommend you address the device aspects of the product as an important next step before you conduct additional clinical studies."

Abbreviations: AKI, acute kidney injury; CDER, Center for Drug Evaluation and Research; CDRH, Center for Devices and Radiological Health; CI, confidence interval; CR, Complete Response; CV, cardiovascular; CVOT, cardiovascular outcomes trial; EOP2, end-of-Phase 2; ET, end treatment; FD&C Act, Food, Drug and Cosmetic Act; FDRR, Formal Dispute Resolution Request; GLP-1, glucagon-like peptide 1; GMP, good manufacturing practices; HR, hazard ratio; ITCA 650, exenatide in DUROS device; ITT, intent-to-treat; MACE, major adverse cardiovascular event; MI, myocardial infarction; NI, noninferiority; NOOH, notice of opportunity for a hearing; OCHEN, Office of Cardiology, Hematology, Endocrinology and Nephrology; OND, Office of New Drugs; PDUFA, Prescription Drug User Fee Act; PK, pharmacokinetics; RA, receptor agonist

5.4 Additional Efficacy Information

CDER statistical reviewers identified several issues with the Applicant's efficacy analyses in the original NDA submission. Details on each issue are presented in the first bullet point under each numbered item below, and the CDER reviewer's approach to address each issue is explained in the corresponding second bullet point.

1. Exclusion of subjects who received study treatment but did not return for the first study visit from the primary efficacy analysis set

    a. For both Study CLP-103 and CLP-105, the primary efficacy analyses were based on what the Applicant termed a "modified intent-to-treat" (mITT) population, defined as subjects who received an initial device placement and had valid baseline data with at least one postbaseline A1C value. In the Applicant's analyses subjects who were randomized and treated, but discontinued treatment before the first visit, were excluded from the primary analysis set. This practice does not adhere to the intent-to-treat (ITT) principle, by which all randomized subjects should be included in the analysis set, and it could introduce bias into the study results (e.g., if there were differences among study subjects who discontinued treatment in the ITCA 650 treatment arms versus comparator arms).
    b. The CDER reviewer conducted post hoc analyses that included all randomized subjects who received at least one dose of the study treatment under the ITT principle.

2. Excluding measurements taken after subjects received rescue therapy

    a. The Applicant's primary analysis excluded measurements collected after subjects received rescue medication. CDER recommends an estimand framework, which employs the treatment policy strategy to handle intercurrent events: i.e., all data regardless of intercurrent event should be included in the primary analysis.
    b. The CDER reviewer conducted post hoc analyses that included all available observations, including data collected after rescue medication.

3. Lack of follow up of subjects who discontinued study treatment

    a. All randomized subjects should be followed up until the end of the study regardless of intercurrent events (including treatment discontinuation). In Study CLP-103, only two subjects in the 40 mcg/day arm, two subjects in the 60 mcg/day arm, and two subjects in the placebo arm were followed up after treatment discontinuation. In Study CLP-105 only one subject from the sitagliptin arm was followed up after treatment discontinuation. This resulted in high missing data rates for both Phase 3 studies. Based on the Applicant-specified endpoint visits (for which the CDER reviewer also identified issues; see details in item 5), approximately 20% of subjects from both studies missed their primary endpoint assessment visit.
    b. The CDER review concluded this was a study conduct issue not remediable by post hoc statistical analyses. Both CDER's and the Applicant's analyses are subject to potential bias and large variability due to high missing data rates.

4. Using methods for handling missing data that assume missing data were missing at completely random or missing at random (i.e., last observation carried forward [LOCF] and mixed models for repeated measures [MMRM])

    a. The Applicant used the LOCF method to handle missing data for Study CLP-103 and the mixed model repeated MMRM method for Study CLP-105. The LOCF is a single imputation method that replaces missing values with previously observed values from the same subjects. This method can overestimate the treatment effect while underestimating the variance. The MMRM assumes missing data are missing at random, which is an unlikely scenario for both studies. The preferred method for missing data handling is multiple imputation based on retrieved dropouts, referring to subjects who discontinued the treatment but were followed up for primary endpoint assessment under missing not at random assumption (Wang et al. 2023).
    b. The Applicant did not follow-up subjects who discontinued study treatment (see item 4), and there were very limited data on retrieved dropouts. The CDER reviewer handled missing data by multiple imputation based on baseline washout analysis (i.e., return-to-baseline) as an alternative method.

5. Protocols were not followed with respect to endpoint visit windows

    a. For both Study CLP-103 and CLP-105, the endpoint visit window prespecified in the protocol was ±7 days of the intended visit day in the schedule of assessments. The Applicant labeled the visits by visit number, regardless of when the visit occurred. This resulted in visits being counted at timepoints far from the intended visit day (e.g., a visit at Day 439 was counted as a Week 26 (Day 182) visit).
    b. Considering that the protocol definition for the visit variable would result in a large amount of missing data, the CDER reviewer created a new visit variable based on a visit window of ±25 days from the intended visit day. Based on the reviewer-defined visit window, the missing data rates were 21.3% and 20.9% for Studies CLP-103 and CLP-105, respectively.

After issuing a CR letter on September 21, 2017, CDER received a CR resubmission from the Applicant on September 9, 2019. The Applicant's post hoc analyses in the resubmission are presented as follows:

1. The Applicant redefined the visit windows that start 3 weeks prior to the first visit, and end 3 weeks after the primary endpoint visit. The cutoffs between two visits are defined as (target day 1 + target day 2) ÷ 2. The Applicant reclassified measurements based on this new visit window definition.
2. The Applicant adopted a "modified copy reference" method for missing data imputation. For Study CLP-103, this imputation method used multiple imputation based on placebo subjects who received rescue medication during the treatment period and had primary endpoint observed. For Study CLP-105, the imputation method used multiple imputation based on subjects from both the ITCA 650 and sitagliptin arms who received rescue medication during the treatment period and had primary endpoint observed.
3. For both Study CLP-103 and CLP-105, the Applicant used ANCOVA for primary analyses.
4. For both Study CLP-103 and CLP-105, the Applicant included all randomized subjects receiving treatment in their analyses.

In the CDER statistical review of the 2019 resubmission, the CDER reviewer disagreed with these post hoc analyses. In particular, the modified copy reference imputation method called into question the validity of the analysis results, as it remains unclear whether subjects who received rescue medication and had primary endpoint observed (the data used for imputation) were comparable to those who discontinued treatment and missed the primary endpoint assessment (the data to be imputed). In summary, the conclusions in the original statistical review were maintained after review of the resubmission.