ITCA 650 (EXENATIDE IMPLANT) FOR THE ADJUNCTIVE TREATMENT OF TYPE 2 DIABETES MELLITUS

SPONSOR BRIEFING DOCUMENT

ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

ADVISORY COMMITTEE BRIEFING MATERIALS:

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Abbreviation	Definition
ACE-I	Angiotensin-Converting Enzyme Inhibitor
AE	Adverse Event
AKI	Acute Kidney Injury
ARB	Angiotensin Receptor Blockers
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CAPA	Corrective Actions and Preventative Actions
CDC	Center for Disease Control
CDER	Center for Drug Evaluation and Research
CI	Confidence Interval
CRL	Complete Response Letter
CVOT	Cardiovascular Outcome Trial
DFMEA	Design Failure Mode and Effect Analysis
DPP-4	Dipeptidyl Peptidase-4
eGFR	Estimated Glomerular Filtration Rate
EMDAC	Endocrinologic and Metabolic Drug Advisory Committee
ESRD	End-stage renal disease
FAERS	FDA Adverse Event Reporting System
FDA	United States Food and Drug Administration
FDRR	Formal Dispute Resolution Request
FPG	Fasting plasma glucose
GI	Gastrointestinal
GLP-1 RA	Glucagon-Like Peptide-1 Receptor Agonist
HbA_{1c}	Glycosylated Hemoglobin
HCP	Healthcare Provider
HR	Hazard Ratio
IVR	In Vitro Release
IV	Intravenous
KDIGO	Kidney Disease Improving Global Outcomes
LOCF	Last observation carried forward
LS	Least-Squares
MACE	Major Adverse Cardiovascular Events
MITT	Modified Intention-to-Treat
MI	Myocardial Infarction
NDA	New Drug Application
NSAID	Non-Steroidal Anti-Inflammatory Drug
OOS	Out-of-Specification

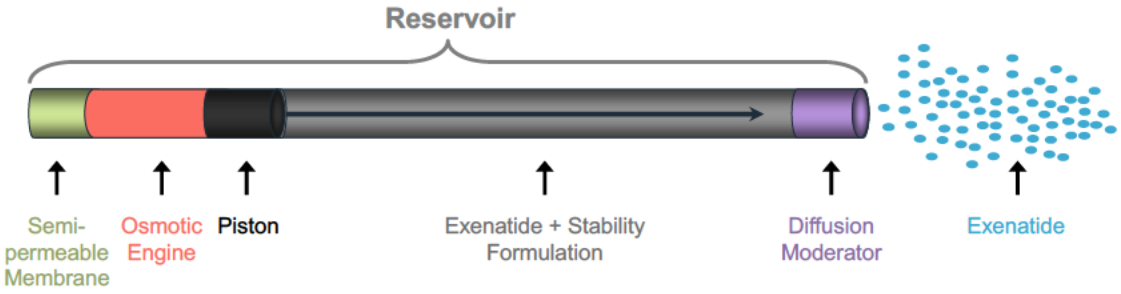
PAI	Pre-Approval Inspection
PI	Prescribing Information or Package Insert
PK	Pharmacokinetic
PST	Process Simulation Test
QC	Quality Control
RRT	Renal Replacement Therapy
SAE	Serious Adverse Event
SCr	Serum Creatinine
SD	Standard Deviation
SE	Standard Error
SGLT	Sodium-Glucose Transporter
SOC	System Organ Class
SU	Sulfonylurea
SWGR	Subassembly Weight Gain Rate
TEAE	Treatment-Emergent Adverse Event
T2DM	Type 2 Diabetes Mellitus
UA	Unstable Angina
US	United States

1 EXECUTIVE SUMMARY

1.1 Introduction

ITCA 650 is an exenatide implant developed by Intarcia Therapeutics for the adjunctive treatment of type 2 diabetes mellitus (T2DM). ITCA 650 would be the only twice-yearly glucagon-like peptide-1 receptor agonist (GLP-1 RA) rigorously tested and designed to help address widespread poor glucose control and medication adherence issues in > 50% of patients suffering from T2DM. ITCA 650, shown in Figure 1, is a small, matchstick-sized implant that would be dosed twice-yearly by a trained healthcare provider in her or her office during routine office visits. ITCA 650 delivers a previously approved GLP-1 RA (exenatide) using technology based on the DUROS® implant technology previously approved for an oncology product (leuprolide acetate, Viadur®).

Figure 1: ITCA 650 Diagram

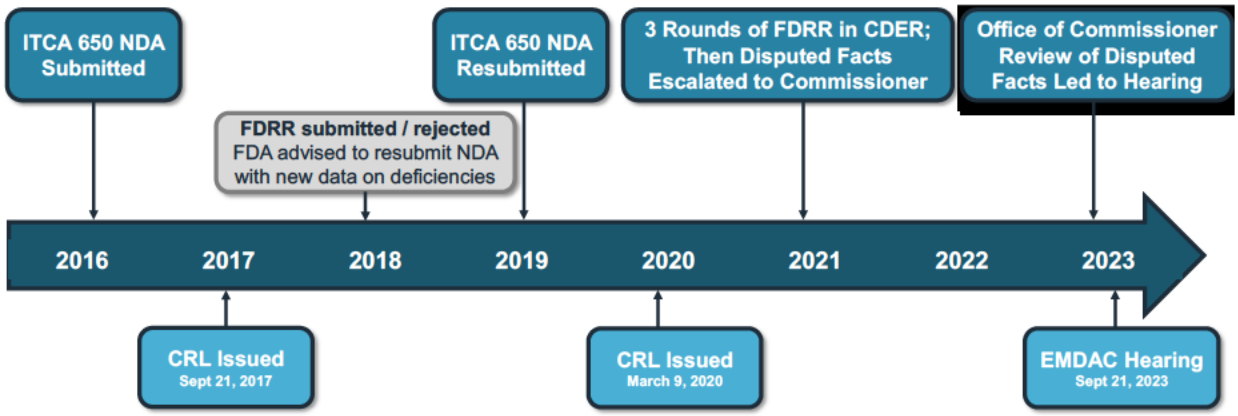


While more than 45 new tablets and injectables have been approved over the last 15 years to treat T2DM, none has been able to address the widespread level of poor glucose control and poor adherence that exists in the T2DM patient community (Edelman 2017). During this time of increased treatment options, including injectable products with less-frequent weekly administration, at least 50% of patients with T2DM remain with uncontrolled glucose control, largely due to non-adherence with their treatments. In the United States (US), we still have > 30% of patients who still have

chronic HbA_{1c} levels > 9% (NCQA 2021, Fang 2021, International Diabetes Federation, Reuters Special Report, Edelman 2017). This has left an unresolved epidemic of unacceptably high morbidity and mortality. ITCA 650 would offer doctors and patients a new maintenance therapy option with proven glucose control with a twice-yearly maintenance dosing interval, providing ensured adherence at 6-month dosing intervals under the supervision and administration by their healthcare provider (HCP). From a patient-centric point of view, it is very important to acknowledge that not all patients will adhere to one main form of drug delivery. ITCA 650 represents a new twice-yearly maintenance therapy option that would now be administered by a trained HCP when poor glucose control and adherence challenges are known health risks with existing therapies.

Intarcia has been pursuing approval of this exenatide implantable dosage form since the first New Drug Application (NDA) submission and complete response letter (CRL) in September 2017. Following resubmission of the NDA for ITCA 650 in 2019 and a second CRL in March of 2020, Intarcia submitted multiple Formal Dispute Resolution Requests, an Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) request (which was denied). Due to substantial factual inaccuracies in the issues stated by the Center for Drug Evaluation and Research (CDER), Intarcia filed a Notice of Opportunity for Hearing request with the Commissioner's Office in March 2021. In February 2023, after thorough reviews of the substantial issues of fact Intarcia submitted vs each of CDER's 6 issues, the Office of the Commissioner and the FDA's Chief Scientific Officer granted Intarcia a public hearing before the EMDAC. FDA's Chief Scientist noted in her letter that "I have identified numerous disputes between the parties…I believe that a public hearing before an advisory committee could aid in the resolution of the parties' disputes and enable the Office of the Commissioner to render a final decision for the agency on this matter." The EMDAC will help resolve the substantial factual disputes between CDER and Intarcia related to the 6 issues cited as the basis for its proposed denial of Intarcia's application (see Table 1 and Table 2).

Figure 2: Intarcia Regulatory Milestones



CDER: Complete Response Letter; FDA: Food and Drug Administration; FDRR: Formal Dispute Resolution within CDER; NDA: New Drug Application

This briefing document serves as background information and facts on record for the hearing before the EMDAC to address each of CDER's proposed reasons to deny approval and AKI labeling options for Intarcia's ITCA 650 application. Each of CDER's concerns is comprehensively addressed. The facts warrant an approval of Intarcia's NDA based on the existing clinical data supporting the application, as well as a class-labeled AKI Warning and a post-approval CVOT commitment.

1.2 Overview of Issues For The Hearing

CDER outlined 6 issues in their public proposal to refuse approval of ITCA 650 (Docket No. FDA–2021–N–0874). The issues relate to clinical benefit-risk, labeling options for AKI, and Chemistry, Manufacturing and Controls (CMC) items. Each of the identified issues contains factual errors, inconsistent application of data interpretation standards, and inconsistent application of GLP-1 class-labeled AKI Warnings and post-approval CVOT Guidance in place at the time.

Items 1–3, summarized in Table 1, are directly linked to the clinical benefit-risk assessment of ITCA 650. ITCA 650 has demonstrated substantial evidence of efficacy (Figure 4) in all 4 Phase 3 trials in the NDA and an overall safety profile that is in-line with exenatide and the GLP-1 class, which includes class-labeled AKI Warnings.

Items 4–6, summarized in Table 2, involve factual clarifications regarding CMC that have been previously addressed by official responses and NDA facts on record with the FDA. Details on each of the CMC-related items can be found in Section 11. The facts document no outstanding issues or clarifications remain to address.

Table 1: Summary of Key Clinical Issues and Documented Facts Publicly Shared in Federal Register

Issue[1]	Facts on Record
Issue #1: AKI Imbalance	
Clinical trials data demonstrated ITCA 650 causes AKI with a numeric imbalance 0.5% vs 0.2%	• Intarcia acknowledges a small numeric AKI SAE imbalance in 1 of 4 trials, in a higher risk renal impaired/CVOT population • GLP-1 GI AEs are a known class effect and an established risk factor linked to pre-renal AKI events in post-marketing reports and CVOTs • FDA's GLP-1 AKI Warnings emphasize the associated role of GI AEs
Magnitude of AKI risk is greater because a numeric imbalance in a RCT is isolated to only ITCA 650	• Sponsors have disclosed AKI SAE numeric imbalances in CVOTs • LEADER CVOT and SUSTAIN-6 CVOTs have unfavorable numeric imbalances in: AKI SAEs, repeat AKI SAEs, deaths, and dialysis • Repeat AKI SAEs have a 14-fold increased risk of ESRD/renal replacement
ITCA 650 subjects had AKI SAEs that led to associated deaths & increased dialysis vs. placebo	• No AKI SAE deaths. No increase in dialysis. All patients recovered. • 2 of 4 AKI SAEs resulted in deaths in the placebo arm
Class labeled AKI Warnings not possible as none of the AKIs had any AKI risk factors noted in labeling	• Each AKI case had both of the class-labeled AKI risk factors • AKI Warnings, monitoring, and risk mitigations can manage AKI risk • An AKI Warning with monitoring and risk mitigations is justified[2]
Issue #2: Major Adverse Cardiovascular Events	
Pre-approval CVOT risk assessment failed to provide sufficient assurance that ITCA 650 is not associated with excess CV risk	• Pre-approval CVOT and meta-analysis met CDER's primary endpoint requirements to progress to a more definitive post-approval CVOT ○ HR = 1.12 (95% CI: 0.83–1.51), $P_{non\text{-}inferiority}$ = 0.002 • Cross-trial comparisons of pre-approval vs post-approval CVOTs 3-4 times larger and longer are unsound and do not replace proper RCTs • A post-approval CVOT is warranted having met FDA's primary endpoint
Issue #3: In Vitro Release	
Clinical data to validate upper & lower limits of device IVR specifications not shown effective and safe for use	• Near 6,000 patients in NDA, 4 successful Phase 3 Trials, > 22,000 implants used throughout Phase 3 trials • ITCA 650 implants delivered within the pre-specified IVR upper and lower limits for the fully intended 3- and 6-months durations • Clinical data in all 4 successful RCTs has validated that the upper and lower limits of IVR-specifications are unequivocally effective, and also shown to be safe for their intended and labeled use • A head-to-head trial vs exenatide (Byetta) at the same daily dose also validated IVR specifications are associated with markedly less GI AEs • Extensive phase 3 data show GI tolerability is in-line with GLP-1 class, and after dose initiation/escalation each GI AE stays < 2% thereafter

AE: adverse event; AKI: acute kidney injury; ARBs/ACEs: angiotensin receptor blockers/angiotensin-converting enzyme; CDER: Center for Drug Evaluation and Research; CVOT: cardiovascular outcomes trial; ESRD: end-stage renal disease; FDA: Food and Drug Administration; GI: gastrointestinal; HR: hazard ratio: IVR: in vitro release; NSAIDs: non-steroidal anti-inflammatory drug; RCT: randomized controlled trial; SAE: serious adverse event

Issue[1]	Facts on Record

[1] CDER's 6 Issues Outlined In Their Public 'Proposed Order' to Deny ITCA 650 Approval With A Version Of Existing GLP-1 Class-Labeled AKI Warnings & A Post Approval CVOT
[2] AKI risk factors: 1) Pre-existing renal impairment and 2) use of concomitant medicines known to increase risk of dehydration and AKI (diuretics, metformin, ARBs/ACEs, NSAIDs)

Table 2: Summary of Key CMC Issues and Documented Facts Publicly Shared in Federal Register

Issue[1]	Facts on Record
Issue #4: Device Failure	
Device reliability and mitigation of failure risks asserted insufficient for effective and safe use	• Device potential failure risks were identified/mitigated to only 0.26%, not 1.46%; The 0.26% was secured via dFMEA work and the normal shift from manual to automated manufacturing during Phase 3 and scale up
Issue #5: Sterility	
Insufficient assurance of sterility	• Facts show sterility control & no deficiencies, including in FDA's final EIR report following our pre-approval manufacturing inspection. • Inspectional information requests completed and on record
Issue #6: Device Quality	
Empty device risk; quality controls; site process simulation tests (PSTs)	• Quality controls, implant filling specifications, and final X-rays of each finished implant ensures no empty devices as seen in extensive IVR tests (3,000 devices tested for full durations and > 22,000 devices used in 4 RCTs) • Passed all manufacturing PSTs / site sterility tests; all PSTs on record

AKI: acute kidney injury; CMC: chemistry manufacturing and controls; CVOT: cardiovascular outcomes trial; DFMEA: design failure mode and effect analysis; EIR: Establishment Inspection Report; FDA: Food and Drug Administration; IVR: in vitro release; RCTs: randomized controlled trials
[1] CDER's 6 Issues Outlined in Their Public 'Proposed Order' to Deny ITCA 650 Approval With A Version Of Existing GLP-1 Class-Labeled AKI Warnings & A Post Approval CVOT

1.3 Clinical Development Program

The ITCA 650 Phase 3 clinical program comprehensively evaluated the efficacy and safety of ITCA 650 through 13 clinical studies yielding data from more than 5,800 patients, with 3,201 patients exposed to ITCA 650. The studies were designed consistent with FDA guidance and precedent from well-accepted clinical study protocols used for other approved T2DM anti-diabetic products (Marso 2016, Marso 2016b, CDER Clinical Review, CDER Medical Review).

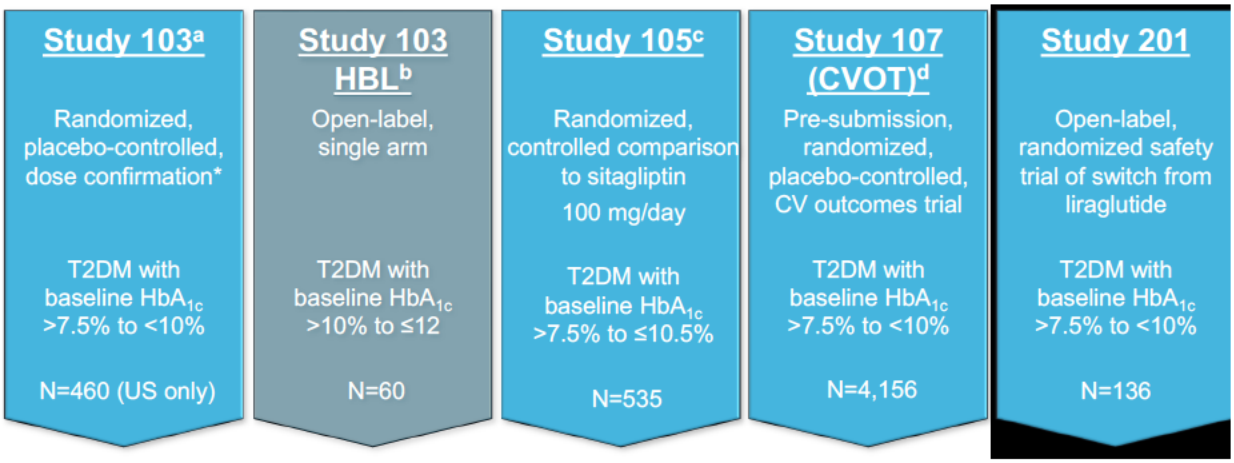
Initial therapy with ITCA 650 is administered as an exenatide 20 mcg/day implant that lasts for 3 months. That is followed by a dose escalation to the maintenance dose where an ITCA 650 60 mcg/day implant is placed for 6 months. ITCA 650 is then removed and replaced with another exenatide 60 mcg/day implant once every 6-months for maintenance therapy.

The effects of ITCA 650 20 mcg/day and 60 mcg/day implants were evaluated in patients with T2DM in multicenter, randomized, controlled, Phase 3 pivotal efficacy studies (Study 103 and Study 105). The NDA also included Study 107 (a pre-approval

CVOT), Study 201 (a switch trial from liraglutide), and Study 103 High Baseline Sub-Study (HBL; in high baseline patients who could not ethically be randomized to placebo; Figure 3).

Additional details on the clinical development program and Studies 103, 105, and 107 are provided in Section 5 and Section 6.

Figure 3: ITCA 650 Key Phase 3 Clinical Studies

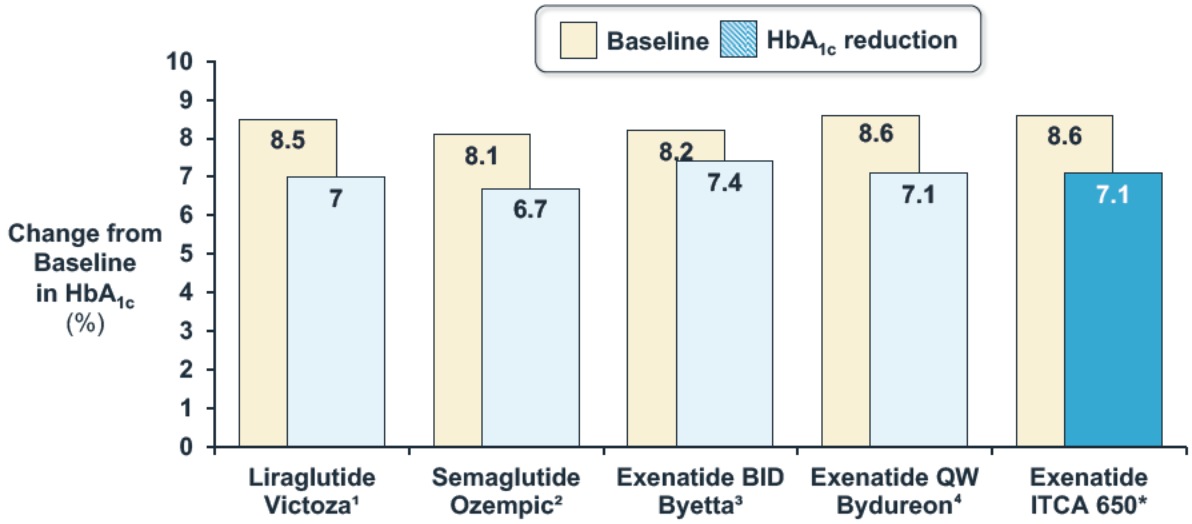


CVOT: cardiovascular outcomes trial; HBL: high baseline between 10-12% HbA_{1c}; T2DM: type 2 diabetes mellitus
* Tested maintenance doses of 40 and 60 mcg/day
a. Rosenstock, ADA Meeting (2015); b. Henry, ADA Meeting (2015); c. Rosenstock, ADA Meeting (2016); d. Ruff et al (2022)

1.4 Efficacy Results

The substantial and sustained glucose lowering efficacy and benefit of ITCA 650 has not been disputed by CDER (Docket No. FDA–2021–N–0874). ITCA 650 has consistently demonstrated substantial and sustained evidence of efficacy at levels that are in-line with approved exenatide injectable products and other approved GLP-1 products (Figure 4).

Figure 4: ITCA 650 Efficacy In-Line with Exenatide and Approved GLP-1s



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

All clinical studies met their primary and secondary endpoints and demonstrated statistically significant and clinically meaningful reductions in HbA_{1c}, body weight, and key HbA_{1c} treatment targets.

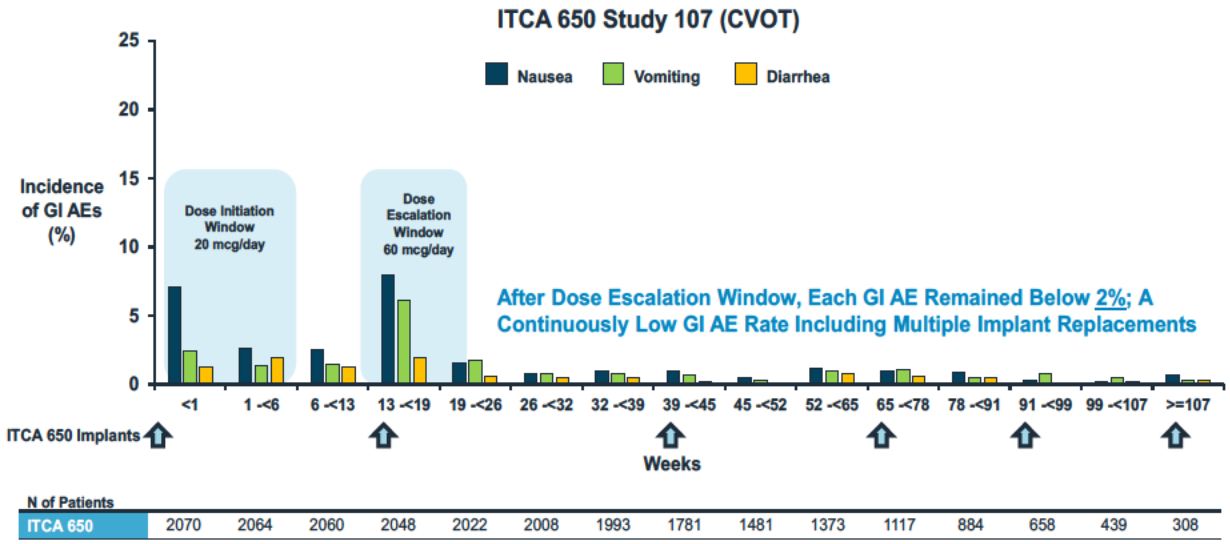
More detailed efficacy results of all key clinical studies are presented in Section 6.

1.5 Safety Results

The safety and overall tolerability profile (including gastrointestinal [GI] adverse events [AEs]) of ITCA 650 aligns with the well-established safety profile of exenatide, as well as other approved GLP-1 RAs, which all include labeled acute kidney injury (AKI) Warnings and Precautions associated with for GI AEs at dose initiation and titration (a class effect).

As with all GLP-1s, the most common AEs observed were GI in nature (e.g., nausea, vomiting, diarrhea). The GI AEs observed were transient in a subset of patients during dose initiation and dose escalation and then declined rapidly after dose escalation to low levels that remained under 2% for maintenance therapy during multiple implant removals and replacements (Figure 5). Also aligned with the class, the majority (> 97%) of GI AEs in the subset of patients that experienced them in the NDA were mild to moderate in severity.

Figure 5: Study 107 Occurrence of Gastrointestinal Adverse Events Over Time



AE: adverse event; CVOT: cardiovascular outcomes trial; GI: gastrointestinal

It is well known and labeled that transient GI AEs can contribute to dehydration, and in patients with known concomitant medications (e.g., diuretics) and other AKI risk factors, can rarely lead to pre-renal AKI events. This pattern of early-on GI AEs around dose initiation and dose escalation is a GLP-1 class effect, and dosing-related GI AEs are highlighted as being associated with the majority of GLP-1 post-marketing AKI events that led to existing class-labeled AKI Warnings and Precautions. Thus, it is important that patients and clinicians understand AKI risk factors and that transient GI AEs and dehydration can occur early-on with GLP-1 products, including ITCA 650. As noted in labeling and published literature, this early-on risk of GI AEs and dehydration in a subset of patients is further exacerbated by concomitant medications which each increase the risk for volume loss, vomiting, diarrhea, and nausea.

Hypovolemia (low blood volume) is the most common cause for AKI and is usually caused by dehydration or excessive bleeding. As a result of dosing-related GI AEs that may contribute to dehydration, all approved GLP-1 products carry an AKI Warning that emphasizes: “Monitor renal function when initiating or escalating doses of [GLP-1] in patients reporting severe adverse GI reactions.”

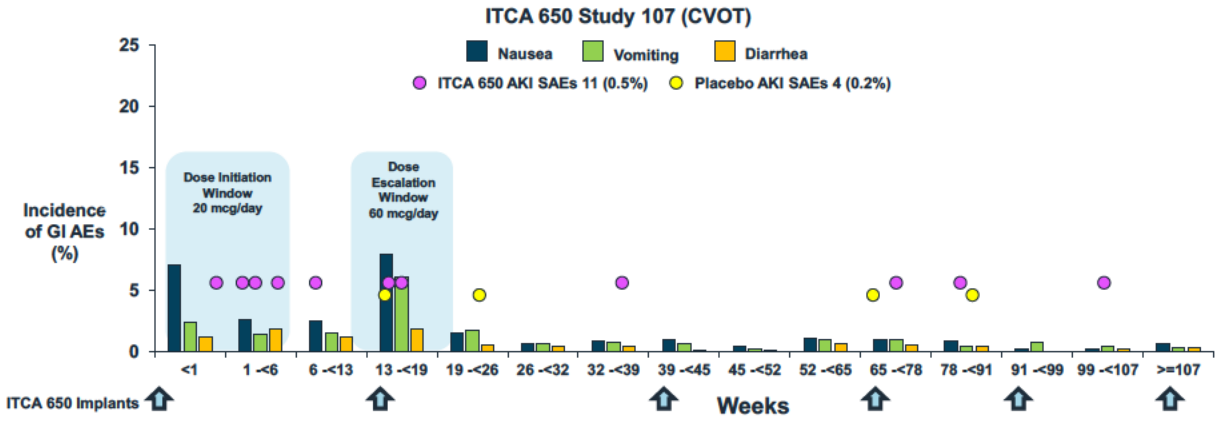
A small numeric imbalance in treatment-emergent AKI SAEs was observed in Study 107 CVOT with 11 events (0.5%) on drug vs 4 events (0.2%) on placebo. Information presented later shows the early timing of the GI AEs and the small numeric imbalance in AKIs mirrors the early-on GI AE pattern for the GLP-1 class and the already highlighted association between early-on GI AEs in the majority of GLP-1 post-marketing AKIs reported to FDA that led to class labeled AKI Warnings for all approved GLP-1 products (Figure 24 and Figure 25).

Each treatment-emergent case of serious AKI in Study 107 also involved the same two concomitant AKI risk factors noted in GLP-1 AKI Warnings (i.e., all patients had underlying renal impairment at baseline and each patient was also using multiple concomitant medications that are known to potentially increase the risk of dehydration and AKI).

Importantly, and based on what has been learned over the years about this AKI pattern for the GLP-1 class in CVOTs and post-marketing events, AKI can be managed, monitored, and mitigated with Warnings and several proactive measures:

- Inform patients about potential early-on GI AEs and the risk of AKI if dehydration occurs; proactively inform patients to stay well hydrated
- Monitor renal function in renal impaired during early dosing windows, especially those with any transient GI AEs; if there is any evidence of dehydration, treat accordingly
- Additionally, if dehydration occurs, modify/stop suspected medications potentially contributing to dehydration (including ITCA 650) and ensure patient gets adequate fluids

Figure 6: Study 107: Transient Gastrointestinal Adverse During Dose Initiation and Escalation Associated with A Small Numeric Imbalance In AKI SAEs



AE: adverse event; AKI: acute kidney injury; ARBs/ACEs: angiotensin receptor blockers/angiotensin-converting enzyme; CVOT: cardiovascular outcomes trial; GI: gastrointestinal; NSAIDs: non-steroidal anti-inflammatory drugs; SAEs: serious adverse events
* ITCA 650 Study 107 (CVOT); AKI risk factors in each case: 1) Pre-existing renal impairment and 2) use of concomitant medicines known impact hydration status, renal function, and AKI risk (diuretics, metformin, ARBs/ACEs, NSAIDS)

Detailed safety results of all key clinical studies are presented in Section 7. AKI and Major Adverse Cardiovascular Events (MACE) are addressed in detail below and in Section 8.

1.6 Review of Clinical Issues and Factual Disputes

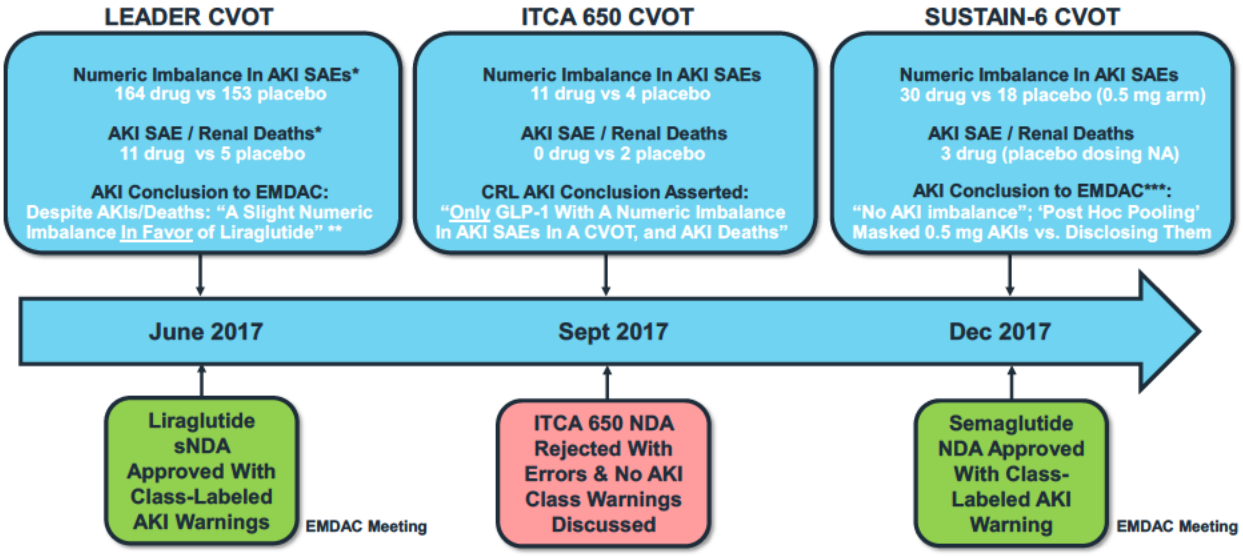
1.6.1 Manageable AKI Risk Exists Across GLP-1 RA Class

Intarcia acknowledges a numeric imbalance in treatment-emergent AKI SAEs (standard MedDRA AKI narrow scope terms) in 1 of the 4 ITCA Phase 3 clinical trials and that all GLP-1 products, including ITCA 650, carry a risk for infrequent AKI events associated with GI AEs during dose initiation and dose escalation as currently emphasized in the labeled AKI Warnings for each GLP-1 product on the market.

The facts on record support that ITCA 650 does not have a new serious AKI signal associated with GI AEs. GI AEs at dose initiation and dose escalation are a class effect and an established risk factor for pre-renal AKI events. Small numeric AKI imbalances are observed in other randomized controlled cardiovascular outcomes trials (CVOTs), and in thousands of post-marketing AKI reports on approved GLP-1 products.

In fact, in 2017 when ITCA 650 was first rejected with AKI as the most concerning issue raised, two other GLP-1 applications with CVOTs containing serious AKI numeric imbalances were taken to EMDAC meetings and approved by CDER (i.e., the liraglutide LEADER CVOT with an AKI SAE numeric imbalance, and the semaglutide SUSTAIN-6 CVOT also contained an AKI SAE numeric imbalance). Both GLP-1s were approved with AKI labeled Warnings and ITCA 650 was rejected, all within a 6-month timeframe in 2017 (Figure 7).

Figure 7: Three GLP-1 Regulatory Applications Reviewed in 2017 with Different Interpretations of AKI SAEs



* Sponsor's AKI SAEs Disclosed in EMDAC Materials (P. 75 of 95); ** CDER's EMDAC Slide 34 ***Sponsor/FDA 'Post Hoc Pooling' Omits 0.5mg arm at EMDAC; Sponsor Disclosed Later @ Clinicaltrials.gov

Published CVOT data and public disclosures of AKI SAEs in liraglutide's LEADER CVOT and semaglutide's SUSTAIN-6 CVOT have shown similarly unfavorable numeric imbalances in AKI SAEs (Figure 26 and Figure 27). Moreover, the identical pattern of early-on GI AEs at dose initiation and dose escalation is associated with the majority of serious AKIs in GLP-1 post-marketing reports. Thousands of serious AKIs associated with early-on GI AEs are documented on GLP-1s in the FDA's safety monitoring database (FDA Adverse Event Reporting System [FAERS]).

Complete details are provided in Section 8.2.

Detailed independent expert evaluation and report showing of AKI SAEs in Study 107 are attached in Appendix Section 13.1.

1.6.2 CV Outcomes Trial Fulfilled Pre-Approval Requirements

The pre-approval CVOT, Study 107, met the FDA primary endpoint required and fulfilled the pre-approval requirements in FDA's Guidance for Industry at the time (FDA CV Risk Guidance). The primary pre-approval analysis of the CVOT trial and meta-analysis of Phase 3 Studies 103 and 105 had a point estimate of HR (95% CI) = 1.12 (0.83 – 1.51) with a $P_{non\text{-}Inferiority}$ = 0.002. Based on known under-powering of pre-approval CVOTs, the data are not definitive; however, FDA's pre-approval primary endpoint requirements were met showing the upper bound of the 95% confidence interval (CI) was < 1.8. Per FDA's intent and Guidance in effect at the time, this result was sufficient as a pre-approval bridge into an adequately powered and longer-duration post-approval CVOT that would be significantly more definitive.

Complete details are provided in Section 8.3.

1.6.3 ITCA 650 In Vitro Release Data Met Upper and Lower Limit Specifications and were Clinically Validated as Effective and Safe in all 4 Successful Phase 3 Trials

The established DUROS® technology used in the ITCA 650 implant met pre-defined in vitro release (IVR) specifications demonstrating consistent release within pre-specified upper and lower IVR limits over the full intended use cycle for the 3- and 6-month implants. The consistent release within IVR specification limits (i.e., upper and lower IVR limits) has been clinically validated with substantial efficacy shown in all 4 Phase 3 randomized, controlled trials (RCTs) and reinforced by a safety profile (e.g., GI AEs, discontinuation rates, pulse rate, hypoglycemia, etc.) that is in-line with exenatide and other GLP-1s including labeled Warnings for AKI.

As summarized in Table 32, the clinical data from all 4 successful RCTs, in nearly 6,000 patients, and the more than 22,000 devices used in Phase 3 trials, clinically validate that the upper and lower IVR release limits are effective and safe for their intended use.

Complete details are provided in Section 8.4.

1.7 Benefit-Risk Summary

A large segment (> 50%) of patients in the US with chronically uncontrolled T2DM (NCQA 2021) need new maintenance therapy and dosing options to help address widespread challenges with poor adherence and poor glucose control which has not improved in the US in well over a decade (Edelman 2017). In fact, > 30% of patients still have HbA_{1c} levels chronically over 9% (NCQA 2021, Fang 2021, International Diabetes Federation, Reuters Special Report, Edelman 2017), which directly impacts a higher rate of morbidity and mortality.

ITCA 650 was specifically designed to combine exenatide, an already-approved and well-studied GLP-1, with a previously approved DUROS implant technology. The data, including a head-to-head trial of ITCA 650 vs exenatide injections early in development, show that the known GI AE risks associated with ITCA 650/GLP-1s are predictably consistent with or better than the approved exenatide injectable product and fully in-line with what is observed in large RCTs and CVOTs with other GLP-1 products.

New extended maintenance dosing options, such as ITCA 650, are needed to address patients' uncontrolled glucose that is largely due to poor adherence with existing options. A twice-yearly maintenance dosing interval (administered by an HCP during routine visits) can be a valuable option to help address very important segments of uncontrolled patients where far too many patients are being left behind with poor glucose control that is largely due to poor adherence with existing options.

ITCA 650 would be the only maintenance therapy option that a trained healthcare provider can administer just twice-yearly when they know chronically uncontrolled glucose and known adherence challenges need to be addressed.

1.8 Substantive Facts on Record Support a Positive Benefit-Risk of ITCA 650 with an Appropriate Class-Labeled AKI Warning and Risk Mitigations.

- ITCA 650 implants are clinically validated as effective and safe for the intended use
    - ITCA 650 has 4 successful RCTs with extensive clinical data validating device IVR upper and lower release limits as effective and safe for their intended use
    - Substantial evidence of efficacy was demonstrated in 4 RCTs with a safety profile in-line with exenatide and GLP-1s with class-labeled AKI Warnings
- Early-on GI AEs are a known GLP-1 class effect and risk factor that is associated with infrequent pre-renal AKIs in several GLP-1 CVOTs and in thousands of GLP-1 post-marketing AKI events reported to FDA.
    - FDA's FAERS database, GLP-1 AKI Warnings, and recent FAERS-related AKI publications specifically emphasize that GLP-1 GI AEs during dose initiation and dose escalation were observed in the majority of AKIs reported to FDA (FAERS database)

  - GI AEs during the same initial dosing windows were associated with the small numeric imbalance in AKI SAEs observed with ITCA 650 in Study 107 (CVOT)
  - Small numeric imbalances AKI SAEs were also publicly disclosed over time related to liraglutide's LEADER CVOT (LEADER EMDAC – Sponsor Briefing Document) and semaglutide's SUSTAIN-6 CVOT (SUSTAIN-6 CT.gov) where the EMA's public medical review noted that AKIs were also temporally associated with GI AEs and dehydration (FAERS database, Dong 2022, EMA SUSTAIN-6 Review)

- ITCA 650 facts show that a GLP-1 class-labeled AKI Warning should be granted
  - Numeric imbalance in 1 of 4 RCTs in a higher risk renal impaired/CVOT
  - Factual corrections on record show no AKI SAE deaths and no increase in dialysis on drug; the only two AKI SAE deaths were on placebo
  - Factual corrections for AKIs also show each of the 11 treatment-emergent AKI cases in Study 107 (CVOT) involved the same concomitant AKI risk factors noted in existing AKI labeled Warnings for all approved GLP-1 products (i.e., underlying renal impairment at baseline and use of certain concomitant meds that impact hydration status and renal function and can contribute pre-renal AKI risk on their own)
  - GI AEs associated with pre-renal AKI events are a GLP-1 class-effect and can be labeled, monitored, and proactively mitigated based on learnings from Study 107, other GLP-1 CVOT trials, and labeled mitigations already in place
- And last, ITCA 650 should be granted a properly designed post-approval CVOT
  - FDA's pre-approval CVOT endpoint requirement was met in Study 107 as a bridge into a more definitive (i.e., a larger, properly powered, and longer duration) post-approval CVOT

2 BACKGROUND ON TYPE 2 DIABETES MELLITUS

Summary

- T2DM, a progressive chronic disease, is a major global epidemic leading to micro- and macrovascular related morbidity and mortality. Using 2019 data, the CDC estimated that over 11% of US population had T2DM (CDC: Diabetes in America).
- The main goal of treatment is to achieve and sustain optimal glycemic control goals and delay the onset and progression to complications, including cardiovascular disease, retinopathy, neuropathy, and nephropathy.
- Over the last decade, at least 50% of patients with T2DM in the US have remained with uncontrolled glucose largely due to non-adherence to existing daily and weekly treatment options available (Edelman 2017).
  - There are still > 30% of patients suffering from uncontrolled T2DM with HbA_{1c} levels > 9% associated with unacceptably high morbidity and mortality.
- While available therapies have helped many patients, there are clear segments of patients who need new and extended maintenance dosing interval options that are fundamentally designed to not be reliant upon self-administration and adherence to daily or weekly treatments. Doctors and certain patients need new maintenance options for uncontrolled glucose and poor adherence.
- Risk benefit determinations should take these unmet needs into account.

2.1 Overview of Type 2 Diabetes Mellitus

2.1.1 Pathology and Epidemiology

While notable progress in the fight against diabetes and its complications has been made, T2DM continues to be a major global epidemic. The International Diabetes Foundation Diabetes Atlas (2021) reports that 10.5% of the global adult population (20–79 years) has diabetes, with almost half unaware that they are living with the condition (International Diabetes Federation). An article recently published in The Lancet states that by 2050 more than 1.31 billion people are projected to have diabetes worldwide, the vast majority being type 2 diabetes (GBD 2021 Diabetes Collaborators 2023). Furthermore, “there is an urgent need to tackle adverse trends in the prevalence of risk factors for type 2 diabetes…without new and far-reaching approaches targeting not only risk factors but also the social and logistical barriers that limit access to treatment and medical attention, diabetes will continue to exert increasingly negative effects on the quality of life of individuals, health of populations, and the strength of global economies for decades to come” (GBD 2021 Diabetes Collaborators 2023). The estimated

prevalence of T2DM in the US, including undiagnosed cases, numbers approximately 37.3 million people (or 11.3% of the population) that had diabetes mellitus in 2019 (CDC). As such, T2DM remains one of the most devastating and costly public health crises (International Diabetes Federation, NCCDPHP).

2.1.2 Symptoms, Morbidity, and Mortality

T2DM is a progressive, chronic disease associated with insulin resistance and loss of pancreatic beta-cell function that leads to hyperglycemia, subsequent multi-organ complications, and increased mortality (DeFronzo 2009). In addition to hyperglycemia, risk factors associated with complications from diabetes include smoking, overweight / obesity, physical inactivity, high blood pressure, and hyperlipidemia (CDC). At least 68% of adults > 65 years of age with diabetes die of heart disease and 16% from stroke. Heart disease death rates among patients with diabetes are 2 to 4 times higher than those in adults without diabetes (Benjamin 2018).

Furthermore, sub-optimal adherence to currently available T2DM medications not only prevents patients from achieving and sustaining their HbA_{1c} goals but also significantly increases morbidity and mortality, more than doubling the risk of hospitalization and increasing the risk of all-cause mortality by 39% (Sokol 2005; Ho 2006). In addition, poor medication adherence has a significant impact on healthcare costs (Banerji 2013; Kennedy-Martin 2017). Greater adherence to diabetes drugs is linked to lower hospitalization rates and could potentially save the US nearly 5 billion dollars per year (Jha 2012).

2.1.3 Current Treatment Options

For now, metformin remains the first-line drug of choice for many patients, after diet and exercise. Current evidence-based treatment guidelines have evolved to include newer pharmacological classes such as GLP-1 RAs, sodium-glucose co-transporter 2 (SGLT-2) inhibitors, and dipeptidyl peptidase 4 (DPP-4) inhibitors as options to add to metformin when additional therapy is needed. Each of these non-insulin pharmacological agents target one or more metabolic defects / pathologies in T2DM (ADA 2019; Davies 2018).

Incretin-based therapies have emerged as important therapeutic agents in the treatment of T2DM. These agents exert their effect primarily by targeting the receptor for the incretin hormone GLP-1, which is released by enteroendocrine cells in the gut and has been shown to augment glucose-dependent insulin secretion in response to nutrient intake. In patients with T2D, pharmacological concentrations of GLP-1 can render the β-cell competent to secrete insulin in response to both glucose and GLP-1 (Kjems 2003).

GLP-1s stimulate the GLP-1 receptor and promote GLP-1 receptor signaling while DPP-4 inhibitors prevent the proteolytic degradation and inactivation of the endogenously released GLP-1, thereby enhancing the systemic concentration of active

GLP-1 (Nauck 2016). The intrinsic risk of hypoglycemia is low for both DPP-4 inhibitors and GLP-1 Ras due to their glucose-dependent mechanism of action. In addition to providing glycemic lowering benefits, clinically meaningful weight loss, and improvements in β-cell function, when GLP-1 RAs have been evaluated in well powered and longer-duration CVOTs designed to evaluate both safety and potential for CV benefit, they have all been proven to be safe. Furthermore, with sufficient power and duration of therapy in post-approval CVOTs, several have been proven beneficial on reducing CV events when extended exposures to treatment and adequate adherence were observed (LEADER EMDAC – Sponsor BD, LEADER EMDAC – FDA BD). Exenatide was not inferior and nearly established as beneficial as well (p=0.002 for non-inferiority and p=0.06 for superiority), despite 43% of patients pre-maturely discontinuing therapy in the EXSCEL CVOT, due largely to documented adherence challenges with the first-generation injectable delivery system (Holman 2017).

Exenatide, as brand names Byetta® (twice-daily injections) and Bydureon® (once-weekly injections), is a well-known injectable GLP-1 product that has been used since 2005 to treat patients with T2DM. Liraglutide (Victoza®, approved in 2010), dulaglutide (Trulicity®, approved in 2014), semaglutide (Ozempic®, approved in 2017, and Rybelsus®, approved in 2019), and tirzepatide (Mounjaro®, approved in 2022) are other GLP-1s indicated as adjunct to diet and exercise to improve glycemic control in patients with T2DM. All but the Rybelsus tablets are administered as subcutaneous injections; liraglutide is administered once daily and dulaglutide, semaglutide, and tirzepatide are administered once weekly. Pharmacological agents in the GLP-1 class, including exenatide, have become important therapeutic options for the treatment of T2DM due to their well-established safety and efficacy profiles (ADA 2019).

2.2 Patient Unmet Medical Need

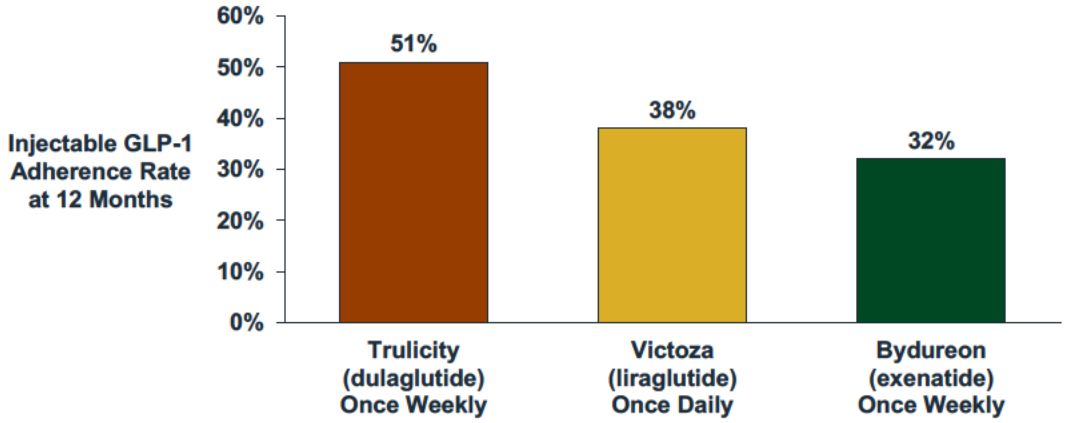
As noted, despite the approval of more than 45 new T2DM tablets and injections over the last 15 years (FDA 2022), > 50% of treated patients are still living with uncontrolled type 2 diabetes. These patients have inadequately controlled glucose levels, and due to the progressive nature of the disease and poor medication adherence over time, they remain a significant risk for increased morbidity and mortality. A National Diabetes Statistics Report in 2020 shows that only ~ 50% of patients in the US were treated to target HbA_{1c} of < 7.0% (CDC 2020). In addition, the prevalence of patients in the US with poorly controlled T2DM (HbA_{1c} > 9%) has remained unacceptably large (> 30%) and virtually unchanged over the past decade up to the latest 2021 results (NCQA 2021, Fang 2021, International Diabetes Federation, Reuters Special Report, Edelman 2017).

2.2.1 Poor Adherence with Currently Available Therapies

Currently available therapies for T2DM have poor rates of medication adherence, with less than 50% of patients remaining adherent to oral or injectable T2DM medications during a 12-month period (Figure 8) (Farr 2014). Poor adherence rates, defined as

patients taking less than 80% of prescribed medication, also exists in > 50% with injectable GLP-1 RA therapies, including once-weekly GLP-1 injections during a 6–12-month period (Guerci 2019, Mody 2018).

Figure 8: Adherence a Key Issue Despite Availability of Multiple GLP-1s



GLP-1: Glucagon-Like Peptide-1
Source: 1. Mody R, Huang Q, Yu M, et. Al. Comparative Glycemic Effectiveness of Dulaglutide vs Liraglutide and Exenatide QW in a US Real-World Setting. Abstract 1071-P. Presented at 78th American Diabetes Association Scientific Sessions; June 22–26, Orlando, FL.
2. Mody R, Huang Q, Yu M, et. Al. Dulaglutide has Higher Adherence and Persistence than Liraglutide and Exenatide QW: 1-year Follow-up from US Real-World Data. Abstract 1264-P. Presented at 78th American Diabetes Association Scientific Sessions; June 22–26, Orlando, FL.
3. Type 2 Diabetes in the Real World: The Elusive Nature of Glycemic Control
https://care.diabetesjournals.org/content/40/11/1425?rss%253D1%2526ssource%253Dmfr=
Note: Adherence is defined as patients taking at least 80% of prescribed medication.

Publications show the reductions in HbA_{1c} observed in the real-world setting were ~50% less for patients treated with GLP-1 RAs and DPP-4 inhibitors compared to patients treated with the same medications in a randomized controlled trial setting (Edelman 2017). Sub-optimal medication adherence was estimated to account for ~75% of the gap in efficacy between clinical trials and real-world results for both drug classes. Adherence in this analysis was defined as ≥ 80% of patients taking their medicine as prescribed during the year following drug initiation.

Due to its multifactorial and complex nature, poor medication adherence represents a difficult set of challenges and behaviors to change without providing product solutions that by design can ensure intrinsic adherence advantages for longer treatment durations than existing daily or weekly products. A systematic review concluded that the majority of previous strategies employed to increase medication self-administration and adherence behaviors have been unsuccessful and unsustainable over time (Sapkota 2015).

While there are multiple injectable GLP-1 RA delivery systems approved, annual adherence and control rates have not improved in North America or around the world over the last decade.

Sub-optimal glycemic control and poor medication adherence results in poor health outcomes and has a significant impact on society due to increased healthcare resource utilization and cost (Sokol 2005; Asche 2011, Edelman 2017, Davies 2018). The lack of medication adherence and glycemic control increases the risk of microvascular and macrovascular complications, and increased morbidity and mortality (Asche 2011; Boye 2016; Buysman 2015; Curtis 2017; Davies 2018; Giorgino 2018; Ho 2006).

3 ITCA 650 PRODUCT DESCRIPTION & DATA HIGHLIGHTS

Summary

- ITCA 650 is a small, 44 mm, sterile, non-biodegradable (titanium), subdermal osmotic implant placed 2–3 mm below the dermal layer in one of the four quadrants of the abdomen by a trained and certified HCP.
- The single-use drug implant combination product delivers a continuous and consistent subcutaneous dose of exenatide for either 3- or 6-months.
  - Exenatide is an approved GLP-1 (since 2005) used for treatment of T2DM.
  - The implant has an osmotic mini-pump functioning inside a titanium cylinder that was previously used in an FDA-approved product (leuprolide acetate).
  - The implant holds sufficient drug product to provide continuous and controlled delivery of exenatide for a 3-month initial period, followed by a once every 6-months maintenance dosing interval.
- The proposed indication of ITCA 650 is as an adjunct to diet and exercise to improve glycemic control in adults with T2DM.
- ALL ITCA 650 implants tested in clinical lots met the pre-specified IVR upper and lower limit release specifications (per USP <724>) and consistently delivered exenatide for the full in-use period of 3-month (initiation of therapy implants) or 6-months (maintenance therapy implants).
- Clinical data from 4 successful Phase 3 trials validated that the implant upper and lower IVR limits are highly effective and safe for their intended/labeled use.
- All manufacturing site process simulation sterility tests (PSTs) for the manufacture of ITCA 650 met acceptance criteria and passed throughout the entire development program.

3.1 ITCA 650 Overview

ITCA 650 was designed to help address poor glucose control risks that are largely related to poor adherence to daily or weekly injectable treatments. ITCA 650 would be the first and only maintenance therapy option with a twice-yearly dosing that is administered by an HCP during routine office visits, and not be reliant on patient self-administration when adherence with daily and weekly medications is a known challenge.

ITCA 650 is a small, 44 mm, sterile, non-biodegradable (titanium), subcutaneous implant. The single-use drug-device combination product (Figure 9) delivers a continuous and consistent subcutaneous maintenance dose of exenatide every day for

6-months. Exenatide, an approved synthetic GLP-1 used for treatment of T2DM, is delivered through an osmotic mini-pump functioning inside the small titanium cylinder.

Figure 9: ITCA 650 Implant

Both the active ingredient and the basic engineering and operation of the implant by osmosis are well researched and established. As noted, the osmotic mini-pump technology incorporated into ITCA 650 is based on the proven DUROS® technology that has previously been used in the FDA-approved product Viadur (leuprolide acetate) until the company (Bayer) exited the therapeutic area and stopped distributing the product. Exenatide is currently available as twice-daily injections of Byetta® (20 mcg/d) and as once-weekly (2 mg) injections of Bydureon® /Bydureon Bcise®.

3.2 Proposed Indication

The proposed indication of ITCA 650 is an adjunct to diet and exercise to improve glycemic control in adults with T2DM.

3.3 Proposed Dosing and Administration

ITCA 650 is not self-administered. It is administered and placed by a trained HCP in the subdermal space of the abdomen, and it delivers exenatide to subcutaneous tissues from where it is readily absorbed into the bloodstream.

ITCA 650 is placed in the subdermal tissue in one of the four quadrants of the abdomen. Each ITCA 650 is placed or replaced with the companion ITCA 650 Drug Delivery System™ placement tool and kit specifically designed for use with ITCA 650.

A video showing the ease of the procedure is available on the company website.

The initial dose is one ITCA 650 20 mcg/day implant for 3 months. The maintenance dose is one ITCA 650 60 mcg/day implant for 6 months. ITCA 650 is removed and replaced with a 60 mcg/day implant every 6 months after the initial dose for maintenance therapy.

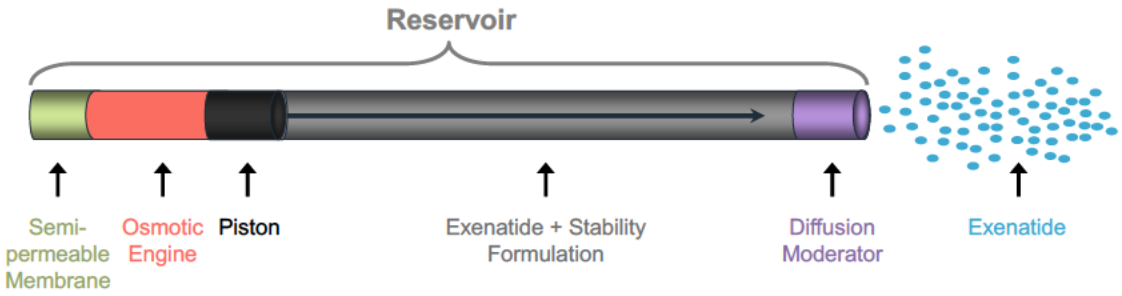
3.4 ITCA 650 Description

3.4.1 Design: Principles of Operation / Mechanism of Action

3.4.1.1 Principles of Operation

ITCA 650 is based on the established DUROS® osmotic implant technology housed in a 4 mm in diameter and 44 mm in length titanium cylinder (Figure 10). Inside the cylinder are a semi-permeable membrane that controls the rate of water intake for the osmotic operation; salt tablets and polyethylene glycol are in the "osmotic engine," which expands as water enters it; a polyethylene piston sits between the osmotic engine and the drug reservoir that holds the stabilized exenatide formulation. At the distal end of the implant is the diffusion moderator through which the drug formulation is expelled. Once the implant is filled and fully assembled in the manufacturing process, the diffusion moderator was designed to not be removeable during any therapeutic use to prevent any risk of dose dumping from the drug reservoir. By intent and purposeful design no such removal of the diffusion moderator or potential dose dumping from the drug reservoir has ever occurred in the program.

Figure 10: ITCA 650 Diagram



The formulation consists of solid exenatide powder suspended in a viscous, non-aqueous vehicle comprised of a polymer-thickening agent dissolved in an organic solvent. The exenatide powder, which also contains sucrose, methionine, and buffer salts as stabilizers, dissolves when it comes into contact with aqueous tissue fluid after the suspension is pushed out of the implant. The exenatide concentration in the formulation is controlled during manufacturing to provide the appropriate exenatide dose and duration for use over 3 months (20 mcg/day) or 6 months (60 mcg/day).

As water crosses the semi-permeable membrane into the salt-filled osmotic engine, the osmotic engine expands, which moves the piston that separates the osmotic engine

from the reservoir that contains the suspension formulation. This process occurs at a very slow and predictable rate dictated by the rate of water influx, which is controlled by the specifications related to the semi-permeable membrane. The moving piston slowly compresses the formulation reservoir, which forces the formulation through the diffusion moderator at the controlled rate into the surrounding subdermal tissues.

ITCA 650 is supplied as a pre-filled, sterile, single-use osmotic implant in a sterile glass vial with a rubber stopper and aluminum tear-off seal. The product is accompanied by a sterile Placement Tool and Placement Guide kit. By design, the viscous property of the suspension limits the potential for exenatide powder settling during use; during storage at controlled room temperature the formulation behaves as a rigid body that effectively prevents settling. At the end of the dosing period, a trained and certified HCP removes and replaces ITCA 650 with another pre-filled mini-pump to continue therapy.

3.4.1.2 Mechanism of Action

The mechanism of action of exenatide (as used in ITCA 650) has been demonstrated in in vitro experiments and in vivo animal studies. Activation of GLP-1 receptors by exenatide induced a cyclic adenosine monophosphate response in a dose-dependent and receptor-dependent manner. Enhancement of glucose-stimulated-insulin secretion, and dose-dependent reduction in HbA_{1c}, glucose, and body weight were observed in Zucker Diabetic Fatty rats (using ITCA 650 and continuous subcutaneous infusion of exenatide) and a dose-dependent weight loss was observed in diet-induced obese rats (using continuous subcutaneous infusion of exenatide). ITCA 650 was also shown to exert secondary pharmacological effects, including reductions in body weight and food consumption, in non-diabetic animals as part of additional nonclinical efficacy and toxicity studies.

3.4.2 Quality Controls and In Vitro Release (IVR) Upper and Lower Limit Testing

As noted, the ITCA 650 uses an established DUROS® osmotic implant technology used with the previously approved product, VIADUR (leuprolide acetate). The same initial weekly and bi-weekly IVR intervals used with ITCA 650 were also used with VIADUR: 0–14 days (Interval 1); 14–28 days (Interval 2); and 28–42 days (Interval 3). As explained in the approval documents for VIADUR, “The time intervals were selected to characterize the implant system in its initial drug release startup phase, and then at steady state.” Further, FDA has accepted “tri-phasic” drug release startup phase followed by a variable release with Bydureon’s injectable depot delivery system, another exenatide product on the market.

Once the implant delivery system reaches steady state, there is a constant delivery of the exenatide formulation at a predetermined delivery rate using the fundamental physics of osmosis. The speed of the piston is determined by the rate of water absorption through the membrane, which was tested by Intarcia and tightly controlled by specifications to deliver the suspension formulation at a constant rate for the intended duration of use (91 days/3 months or 182 days/6 months).

The IVR rate is a key quality attribute that predicts in vivo drug delivery. The critical factors that are controlled and affect IVR include the rate of water uptake by the mini-pump through the semi-permeable membrane, implant manufacturing specifications, and the exenatide concentration in the suspension. The IVR rate is evaluated by measuring the mass of exenatide released in specified time intervals from the implants.

The method used for routine quality control (QC) measurement of the IVR rate of exenatide from ITCA 650 devices was developed and validated for weekly and biweekly measurements and has been used to characterize and verify the design and performance of ITCA 650 devices and for routine QC testing for the devices used in all 4 successful clinical studies in the NDA. Previously approved products using the same DUROS® osmotic implant technology used the same IVR approach and measures as well. The ITCA 650 IVR assay measures the weekly or biweekly exenatide released from ITCA 650 implants.

The IVR data for ITCA 650 implants measures and demonstrates the continuous and consistent release of exenatide within set upper and lower limit specifications for the full in-use period of 3- or 6-months for each implant, show in Figure 31 and Figure 32, respectively.

Delivering exenatide within the pre-specified IVR upper and lower limit specifications (per USP <724>) ensures continuous exenatide delivery that has been clinically validated as highly effective and safe for the intended/labeled use. Substantial evidence of efficacy was established in every clinical trial and the safety and tolerability profile in all 4 RCTs was fully in line with overall AEs and GI AEs that are a known class effect and a labeled risk factor in AKI Warnings for all approved GLP-1 products. Upper and lower IVR limits were evaluated weekly and biweekly throughout the end of the intended in-use life of the product. The clinical and registration lots shared later in Section 8.4.2 demonstrated consistent cumulative release within the pre-specified IVR upper and lower limits.

3.4.2.1 Summary of Release Criteria Enhancements and Quality

After gathering extensive Phase 3 data from all 4 trials, the device in vitro specification limits (i.e., the upper and lower IVR limit specifications) were further tightened in response to a request from CDER during the first NDA review cycle. The IVR data presented in Section 8.4.2.1 (Figure 31 and Figure 32) meets those tightened IVR specifications as shown for the full intended use durations. Each tested implant shown by an individual dot is within specification.

Additionally, the issue of implant failure risks of 1.46% was raised by CDER in Issue #4 (Section 11.1). Implant failure risks were identified per standard design failure mode and effect analysis (DFMEA) procedures, and each was mitigated to a very low level. The cumulative device failure risk data contained in the last NDA submission were only 0.26% (3 out of 1,170 implants assessed). This broke down into 0 devices (0%) with

early piston stoppage, only 1 device (0.09%) with inconsistent delivery within IVR specifications, and 2 devices (0.17%) that had slightly early exhaustion (detected at the end of intended device duration). These very low rates were also achieved with the normal shift from manual to automated manufacturing steps that continue to improve with commercial manufacturing and scale up.

ITCA 650 devices performed as designed to deliver exenatide for the full duration of use and within the established specifications as evidenced by the totality of the clinical program data and by extensive in vitro performance testing on every clinical and commercial lot manufactured throughout the program.

In March 2018, Intarcia received a comment from the FDA requesting Intarcia to do a one-time characterization study of the IVR of ITCA 650 at daily intervals throughout the implant life using a thorough design verification and validation exercise. The FDA wanted Intarcia to reassure that there was not any major daily IVR on any one or two days within the normal weekly or biweekly IVR specifications that had been used throughout Phase 3 trials. Intarcia fully complied with this one-time daily IVR request for the intended commercial ITCA 650 20 mcg/day and 60 mcg/day implants. The new one-time method for daily measurements of IVR (i.e., precise every 24 hours testing for 3- and 6-month pumps) was developed and had to be adapted from that used for weekly measurement and carried out so it could be filed in the NDA resubmission in 2019.

Implant performance met the defined acceptance criteria for target dose delivery, and variations were within the acceptable range for the full in-use periods of 3 and 6 months. For all sampling intervals for each product, acceptance criteria were met with 95% confidence and 80% reliability for the initial week, and 95% confidence and 90% reliability were met for the rest of the in-use period. There was no evidence of any “major daily IVR releases” or outliers on one or two days within a week. Moreover, the Phase 3 devices, whether assessed by the standard weekly or daily IVR methods, are supported by extensive clinical data in all 4 Phase 3 trials as effective and with well characterized safety that is squarely in-line with GLP-1s AE and risks observed and handled with class-labeled Warnings and risk mitigations (e.g., AKI).

The measured daily IVR test results, when cumulated to weekly or biweekly rates, complied with the proposed QC specification. Further, the average delivery rates were comparable between daily and weekly / biweekly measurements.

3.4.2.2 Summary for QC Results Confirming Manufacturing Quality

Context for the quality and manufacturing related information requests noted in Issues 4, 5, and 6 (discussed in more detail in Sections 11.1, 11.2, and 11.3, respectively) is presented below.

Intarcia has rigorous device filling specifications and also implemented additional controls to prevent the release of any empty devices. In addition to filling specifications,

each device is put through X-ray inspection as a last step to ensure no empty devices are in the final finished product. No empty system has been detected or reported among > 3,000 devices tested during IVR studies (evidence provided to FDA). Additionally, substantial and sustained efficacy and no related product complaints in the thousands of devices used in Phase 3 do not indicate that empty systems have occurred in finished product.

All manufacturing site process simulation sterility tests (PSTs) met acceptance criteria and passed throughout the program as the product was manufactured. An additional PST was conducted following the January 2020 Pre-Approval Inspection (PAI) and the additional PST also met acceptance criteria. This was also provided on time in writing to the FDA as requested.

Sterility: ITCA 650 lots are produced under aseptic conditions and are tested for sterility per the USP <71> requirements. The product is implanted under the skin and therefore each product lot must be confirmed to be sterile before it is released.

Endotoxins: The product is tested according to USP <85> and complies with limits of NMT 85 EU/system. This limit provides assurance that the product is free of contamination and will not induce fever or other reactions in a patient due to the presence of bacterial endotoxins.

Subassembly Weight Gain Rate (SWGR): The test for SWGR is a critical in-process control and is conducted on completed subassemblies comprised of the titanium shell, semi-permeable membrane, the osmotic engine including the salt tablets and polyethylene glycol, and the piston. Subassemblies are tested prior to sterilization by gamma-irradiation. The test measures the gain in the weight of the subassembly resulting from the uptake of water after immersing the membrane end of the subassembly into a buffered aqueous solution. The SWGR determines the target loading of the drug in the implant.

Specifications for the SWGR and for the polyurethane raw material used to make the semi-permeable membrane were optimized during development to extend the use period, starting with lots made in 2016:

- The upper SWGR limits for the devices were adapted to ensure release of exenatide for the full duration of the treatment period. The acceptable range for mean SWGR in each lot is 1.3 mg/day to 1.6 mg/day for the 3-month 20-mcg/day product.
- To meet the lower rate of SWGR for the implant membranes, the specification for water gain by the polyurethane raw material was narrowed.

Particle Size Distribution and Content Uniformity: The exenatide spray-dried powder is essentially insoluble in the vehicle and the particle size distribution is controlled to ensure particles are small enough to remain suspended in vehicle and pass through the channel of the diffusion moderator. More than 90% of particles have a diameter less

than 10 μm, which is at least 25 times less than the diameter of the channel in the diffusion moderator and allows the particles to readily pass through the channel during release from the implant. Control of the variation of exenatide concentration between dosage units is assured by testing a specified number of individual dosage units sampled from the batch to conform with USP <905> requirements for content uniformity. The blend uniformity of the suspension is also verified during the filling process.

4 REGULATORY AND DEVELOPMENT HISTORY

4.1 Regulatory History

Key regulatory interactions include:

- 21 November 2016: Intarcia submitted NDA 209053 for ITCA 650 (exenatide implant) for the adjunctive treatment of T2DM. The application included studies demonstrating a statistically and clinically significant reduction in HbA_{1c} compared to both placebo and active controls in multiple adequate and well-controlled clinical studies.
- 21 September 2017: The Agency issued a CRL 1, raising clinical and pharmacokinetic concerns, device and product quality issues, and immunogenicity concerns.
- 16 October 2018: Intarcia submitted a Formal Dispute Resolution Request (FDRR), which was rejected because new information and new analyses were provided. Intarcia was encouraged to resubmit the NDA with the new information.
- 09 September 2019: Based on guidance provided by the FDA during a Type C meeting on 14 May 2019, Intarcia resubmitted NDA 209053 with responses to the issues cited in CRL 1 along with additional clinical data from Study 201, new daily IVR data produced as requested, and new comparative PK data that were requested and modeled vs Bydureon.
- 09 March 2020: The review division issued CRL 2, which described issues related to clinical, device, and product quality concerns. The Agency stated a “numeric imbalance” in AKI SAEs in CVOT Study 107 as their primary concern during the Type A Post-Action Meeting on 20 April 2020.
- July – November 2020: Intarcia subsequently submitted requests for formal dispute resolution to the Office of Cardiology, Hematology, Endocrinology and Nephrology, the Office of New Drugs (, and the CDER, each was denied. Intarcia’s request for an advisory committee meeting was also denied.
- 16 March 2021: Following CDER’s denial of formal dispute resolution and a public advisory committee meeting, Intarcia requested a Notice of Opportunity for Hearing under 21 CFR Part 12 with the Commissioner’s Office. Intarcia submitted a request for hearing in accordance with 21 CFR 314.200l(1) following CDER’s publication of the Notice of Opportunity for a Hearing in the Federal Register.
- 01 November 2021: Intarcia submitted substantial issues of fact, data corrections, information, and analyses in support of its request for a public hearing. Stated issues from CDER and facts from Intarcia were all made in public on the federal register, and > 50 individuals also filed formal responses in support

of ITCA 650 based on facts on record in the NDA and public data. This included multiple prior Presidents of the American Diabetes Association (ADA), top T2DM and GLP-1 experts in the field, patient groups and clinicians and patients.

- 15 February 2022: Intarcia submitted a supplemental submission on the basis of new information that became available publicly.
- 10 August 2022: CDER served Intarcia with a draft proposed order denying Intarcia's public hearing request regarding the proposed denial of the ITCA 650 NDA.
- 10 October 2022: Intarcia responded to CDER's Proposed Order with a comprehensive summary of the substantial issues of factual dispute between the parties on each of the 6 points raised. This was directed to the Office of the Commissioner for a side-by-side review of CDER's Proposed Order and Intarcia's statement of "substantial issues of fact" that Intarcia put forth to justify the basis of a public hearing.
- After a comprehensive review within the Office of the Commissioner, it was noted "numerous disputes were identified between the parties with respect to the NDA for ITCA 650," and the Office of the Commissioner and FDA's Chief Scientist granted Intarcia an alternate form of a public hearing in the form of an Advisory Committee. Intarcia agreed and submitted its request on 20 February 2023, waiving its right to a formal evidentiary hearing in exchange for the opportunity to resolve the fact-based disputes in a public meeting before the EMDAC.
- FDA's Chief Scientist in the Office of the Commissioner will take the output of the public EMDAC hearing as an initial decision and review it with all other public materials in this matter when making a final decision about the ITCA 650 NDA.

5 CLINICAL DEVELOPMENT PROGRAM

Summary

- The clinical development program consists of 13 clinical studies yielding data from more than 5,800 patients, with 3,201 patients exposed to ITCA 650, including some for up to ~50 months in the Study 103 extension study.
- The ITCA 650 Phase 3 clinical program was designed consistent with FDA guidance and precedent from well-accepted clinical study protocols used for other approved T2DM anti-diabetic products.
- The medium to long-term effects of ITCA 650 20/60 mcg/day were evaluated in patients with T2DM from two multicenter, randomized, controlled, Phase 3 pivotal efficacy studies (Study 103 and Study 105) and supported by additional studies (including Study 107, Study 103 HBL, and Study 201).

Intarcia has conducted a comprehensive global clinical development program of 13 clinical studies yielding data from more than 5,800 patients, with 3,201 patients exposed to ITCA 650, including some for up to ~50 months in the Study 103 extension study.

Data from nonclinical and clinical studies contribute to the characterization of the absorption, distribution, metabolism, and elimination profile; the pharmacokinetic and pharmacodynamic effects; and efficacy and safety of ITCA 650. Patients from the US comprised 44% of participants in the clinical program.

The ITCA 650 Phase 3 clinical program (Figure 3) was designed to comprehensively evaluate the efficacy and safety of ITCA 650, as well as to confirm the dosing strategy developed in the Phase 1 and 2 studies. The medium to long-term effects of ITCA 650 20/60 mcg/day were evaluated in a diverse population of patients with T2DM in two multicenter, randomized, controlled, Phase 3 pivotal efficacy studies (Study 103 and Study 105) and supported by additional studies (including Study 107 and Study 103 HBL). These clinical studies contribute key evidence to support the proposed dosing regimen of ITCA 650 20/60 mcg/day.

The randomized studies followed traditional design for studying efficacy and safety in patients with T2DM. Patients on diet and exercise alone, or diet and exercise plus background oral therapy, were randomized to ITCA 650 starting dose of 20 mcg/day or placebo and followed for 13 weeks. At that point, patients are up-titrated to 60 mcg/day for the next 6 months.

The endpoints used for Studies 103 and 105 were commonly used and well-accepted endpoints in diabetes studies and are consistent with the updated 2023 FDA guidance for efficacy endpoints (2023 FDA Efficacy Endpoints Guidance). The primary endpoint

was change from baseline in HbA_{1c}. The CVOT was designed similar to other pre-approval CVOTs, but used time-to-MACE+ as the primary endpoint (which included hospitalization for unstable angina (UA) within the primary composite endpoint) rather than a standard MACE endpoint.

When the pivotal Phase 3 studies were designed, the original protocol-defined primary efficacy analysis method for change in HbA_{1c} and body weight was an analysis of covariance (ANCOVA) model with the last observation carried forward method (LOCF) to handle missing data. A mixed-effect model repeated measures (MMRM) analysis was pre-specified as a sensitivity analysis in the SAP. Based on the most recent feedback from the FDA on Study 103 that the LOCF methodology was no longer the preferred approach to handle missing data, Intarcia updated its analytical approaches for planned and ongoing studies to MMRM.

For Study 103 and Study 103 (HBL), the LOCF ANCOVA approach was retained for the primary analysis of change in HbA_{1c} and body weight because the database had been locked by the time FDA comments were received. These comments/requests were addressed as post hoc sensitivity analyses after database lock. For Study 105, the MMRM model was used for the primary efficacy analysis of change from baseline HbA_{1c} and body weight, and the LOCF method was retained for additional analyses comparing data between the pivotal studies. For Study 107, the MMRM approach was used to analyze the exploratory efficacy endpoints.

Intarcia also considered the clinical study design and dosing regimens of the commercially available exenatide products, both Byetta and Bydureon. The ITCA 650 clinical program was discussed with the FDA, however, it is relevant to point out that Intarcia's original Phase 3 clinical development plans were established and agreed with FDA in 2011 at the time of the End of Phase 2 meeting before FDA settled on various revisions and updates in the preferred efficacy endpoint analyses to address potential missing data. Accordingly, the ITCA 650 pivotal Phase 3 trials were not designed to collect data after discontinuation of therapy, which has led to the proposal of a more equitable and balanced efficacy sensitivity analyses to confirm the results of primary and secondary efficacy endpoints described in clinical study reports of the pivotal studies in the absence of sufficient retrieved dropout clinical data. In the NDA resubmission, Intarcia added a complete array of efficacy sensitivity analyses, including methods requested by FDA and as suggested during the 14 May 2019 Type C meeting, in order to evaluate the robustness of the efficacy results from the ITCA 650 Phase 3 pivotal trials submitted in the original NDA. These sensitivity analyses strongly supported the substantial and unequivocal evidence of efficacy in all 4 RCTs in the NDA. FDA has not disputed the substantial evidence of efficacy in any of the ITCA 650 trials.

6 PHASE 3 CLINICAL EFFICACY

Summary

- Unequivocal and sustained glucose lowering (HbA_{1c}) efficacy of ITCA 650 has been established across all 4 successful and well conducted Phase 3 studies.
- The randomized studies followed traditional designs for studying efficacy and safety in patients with T2DM.
- All randomized, controlled studies met their key pre-specified clinical endpoints, demonstrating statistically significant and clinically meaningful and sustained reductions in HbA_{1c}, body weight, and key HbA_{1c} treatment targets.

6.1 Pivotal Phase 3 Efficacy Study 103

6.1.1 Study Design

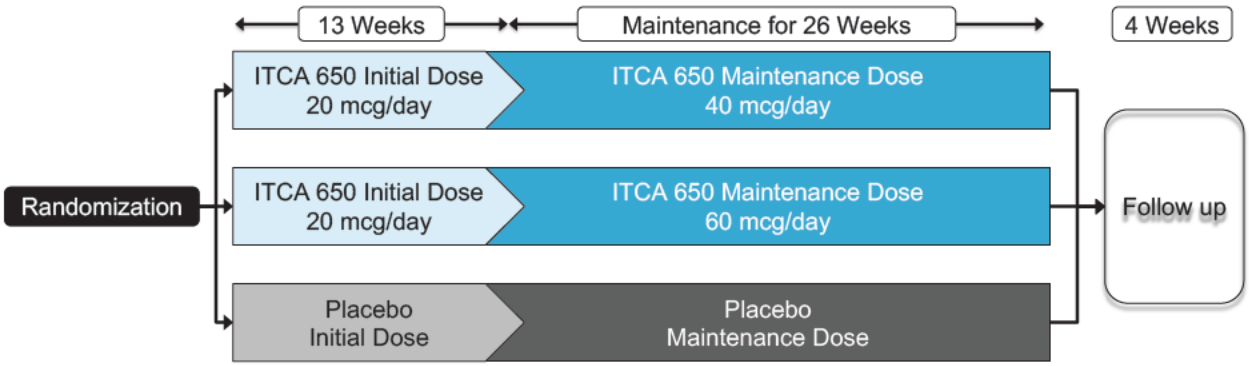
6.1.1.1 Overview

Study ITCA-650-CLP-103 (Study 103) was a pivotal, US-only, randomized, double-blind, placebo-controlled, multicenter Phase 3 study designed to evaluate the efficacy, safety, and tolerability of ITCA 650 (20/40 mcg/day and 20/60 mcg/day) compared to placebo for up to 39 weeks.

Eligible patient populations for the pivotal efficacy study, Study 103, included adults who had T2DM diagnosed ≥ 3 months prior to screening, had measured screening HbA_{1c} levels between 7.5% and 10.0%, and were at a body mass index (BMI) between 25 to 45 kg/m^2, inclusive.

The study consisted of 3 periods: a 4-week screening period; a 39-week, double-blind, placebo-controlled treatment period that included a 13-week period with an introductory dose of 20 mcg/day (or ITCA placebo) followed by a 26-week period (i.e., 6 month implants) of either ITCA 650 40 mcg/day or ITCA 650 60 mcg/day (or ITCA placebo); and a 4-week safety follow-up period (Figure 11). Eligible patients were randomized 1:1:1 to ITCA 650 40 mcg/day, ITCA 650 60 mcg/day, or ITCA placebo. The intended comparisons for each active arm were against the ITCA 650 placebo arm. Both initial doses of ITCA 650 were initiated with the 20 mcg/day implants for the first 3 months. Patients were stratified by concomitant sulfonylurea (SU) use.

Figure 11: Study 103 Design



The primary endpoint was:

- Change in HbA_{1c} (%) between Week 39 and Day 0

Secondary endpoints included:

- Change in body weight (kg) between Week 39 and Day 0
- Proportion of patients with HbA_{1c} < 7% measured at Week 39

6.1.2 Patient Population

Patient disposition, demographics, baseline characteristics, diabetes history, and medical history were similar across the treatment groups. The reported medical history was generally characteristic of what would be expected for patients with T2DM and was comparable across the treatment groups. Nearly all patients (99.6%) were taking concomitant medications. Most patients (89.1%) were taking background anti-diabetic medications at baseline. There were no notable differences in background anti-diabetic medication use at baseline across the 3 treatment groups.

6.1.3 Primary Efficacy Results

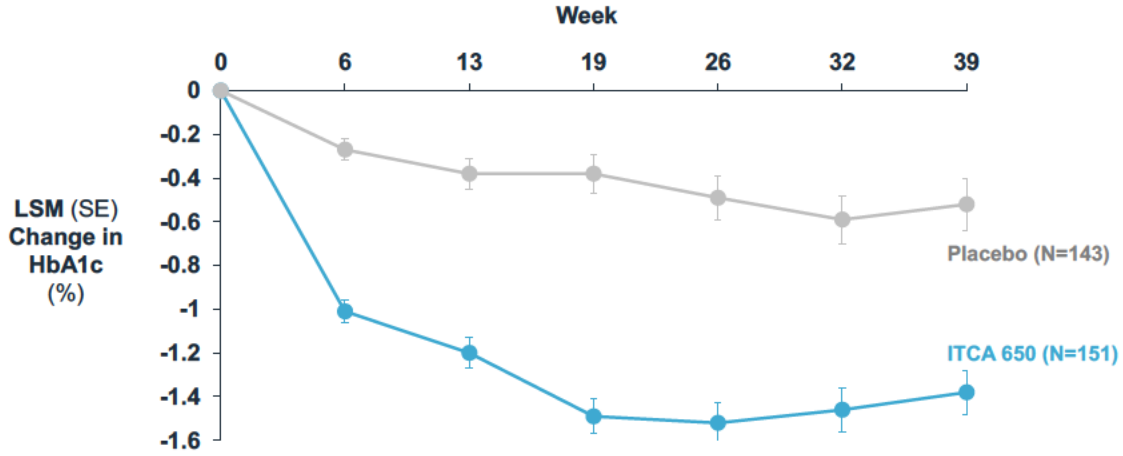
Results of the primary endpoint analysis showed statistically ($p < 0.001$) and clinically significant decreases in HbA_{1c} with each dosing arm (60 mcg/day and 40 mcg/day implants) of ITCA 650 compared with ITCA placebo following 39 weeks of treatment (Table 3). Significant differences between each ITCA 650 dose group and ITCA placebo were already evident by Week 6. These effects were enhanced with greater reductions on the maintenance doses and were sustained throughout the treatment period and were statistically significant at 39 weeks (Figure 12). The 60 mcg/d arm outperformed the 40 mcg/d arm on measures of % of patients with HbA_{1c} below 7%, fewer patients requiring rescue therapy, and weight loss without any clinically meaningful differences in AEs. The 6-month 60 mcg/day maintenance dose was the dose used in all the 3 other RCTs in the NDA.

Table 3: Study 103 Statistical Analyses on Change from Baseline HbA1c (%) at Week 39

Analysis Model and Population	HbA_{1c} LS Mean and LS Mean Difference at Week 39		
	ITCA 650 20/40 mcg/day (N = 147)	ITCA 650 20/60 mcg/day (N = 151)	Placebo (N = 143)
Baseline HbA_{1c} (%)			
Mean (SD)	8.5 (0.788)	8.44 (0.780)	8.50 (0.793)
Median (Min, Max)	8.40 (7.0, 10.8)	8.40 (6.9, 10.3)	8.50 (7.1, 10.3)
ANCOVA at LOCF Endpoint (mITT): pre-specified primary analysis[a]			
LS Mean (SE)	-1.12 (0.090)	-1.20 (0.089)	-0.12 (0.091)
LS Mean Difference, 97.5% CI	-1.00 (-1.29, -0.71)	-1.09 (-1.37, -0.80)	
p-value (vs placebo)	< 0.001	< 0.001	

ANCOVA: analysis of covariance; CI: confidence interval; HbA_{1c}: glycosylated hemoglobin; LOCF: last observation carried forward; LS: least-squares; mITT: modified intention-to-treat; n: number of patients included in the analysis calculation (depended on analysis method); N: total number; SD: standard deviation; SE: standard error
Note: LS mean difference = LS mean active treatment – LS mean placebo.
Note: Baseline is defined as the last assessment on or before the day of the initial placement procedure of ITCA 650/placebo.

Figure 12: Study 103 Mean Change (± 2 SE) from Baseline HbA1c (%) During the Treatment Period – mITT



HbA1c: glycosylated hemoglobin; mITT: modified intention-to-treat; SE: standard error
40 mg data not shown.
Note: The error bars represent the average measurement plus and minus 2 times the SE.

6.1.4 Secondary Efficacy Results

After 39 weeks of treatment, statistically significant and clinically meaningful decreases in body weight from baseline were observed with each dose of ITCA 650 compared with ITCA placebo (Table 4 and Figure 13). The proportion of patients achieving target

HbA_{1c} < 7% at LOCF was also statistically greater for the two ITCA 650 dose groups compared with ITCA placebo (Table 5).

Table 4: Study 103 Statistical Analyses on Change from Baseline Body Weight at Week 39

Analysis Model and Population	ITCA 650 20/40 mcg/day (N = 147)	ITCA 650 20/60 mcg/day (N = 151)	Placebo (N = 143)
Baseline Body Weight (kg)			
Mean (SD)	96.68 (18.503)	97.70 (18.268)	97.25 (21.626)
Median (Min, Max)	96.16 (51.9, 145.0)	97.00 (53.9, 136.9)	96.40 (56.9, 154.9)
ANCOVA at LOCF Endpoint (mITT): pre-specified primary analysis[a]			
LS Mean (SE)	-2.31 (0.365)	-3.01 (0.361)	-1.04 (0.370)
LS Mean Difference, 97.5% CI	-1.27 (-2.44, -0.10)	-1.97 (-3.13, -0.81)	
p-value (vs placebo)	0.015	< 0.001	

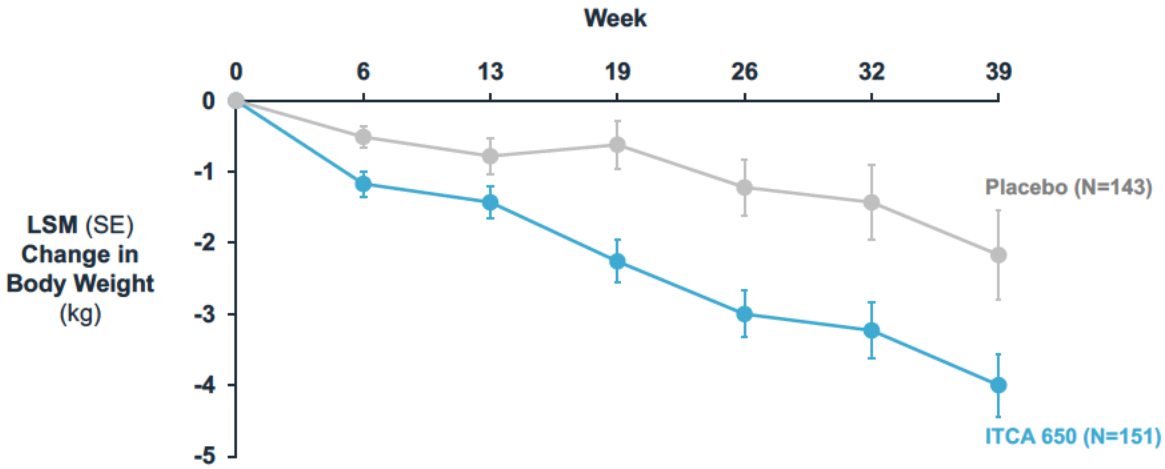
ANCOVA: analysis of covariance; CI: confidence interval; HbA_{1c}: glycosylated hemoglobin; LOCF: last observation carried forward; LS: least-squares; mITT: modified intention-to-treat; n: number of patients included in the analysis calculation (depended on analysis method); N: total number; SD: standard deviation; SE: standard error

Note: LS mean difference = LS mean active treatment – LS mean placebo.

Note: Baseline is defined as the last assessment on or before the day of the initial placement procedure of ITCA 650/placebo.

[a] Pair-wise comparisons (2-sided p-values) for each treatment group versus placebo are based on LS means from an ANCOVA model with the change in body weight at LOCF Endpoint as the outcome variable and treatment, baseline body weight (kg) and sulfonylureas stratification based on randomization as explanatory variables. The p-value for a particular treatment group comparison can only be assessed for significance if the change from baseline HbA_{1c} (%) at the LOCF Endpoint is significant at alpha = 0.025 for that treatment group comparison. Data after the patient received rescue therapy were imputed by using the LOCF method.

Figure 13: Study 103 Mean (± 2 SE) Change from Baseline Body Weight (kg) During the Treatment Period (mITT Population)



LOCF: last observation carried forward; mITT: modified intention-to-treat; SE: standard error.
40 mg data not shown

Note: The error bars represent the average measurement ± 2 times the SE.
Note: Missing values were imputed using the LOCF method when determining the LOCF Endpoint. Patients who took rescue therapy were included with their last post-baseline HbA_{1c} value before beginning rescue therapy carried forward.

Table 5: Study 103 Proportion of Patients with HbA1c < 7% at LOCF Endpoint (mITT Population)

	ITCA 650 40 mcg/day (N = 147)	ITCA 650 60 mcg/day (N = 151)	Placebo (N = 143)
LOCF Endpoint HbA_{1c}			
< 7.0%	55 (37.4%)	66 (43.7%)	13 (9.1%)
≥ 7.0%	92 (62.6%)	85 (56.3%)	130 (90.9%)
Odds Ratio	6.446	8.146	
97.5% CI of Odds Ratio	(2.985, 13.921)	(3.799, 17.469)	
p-value (vs Placebo)	< 0.001	< 0.001	

CI: confidence interval; HbA_{1c}: glycosylated hemoglobin; LOCF: last observation carried forward; mITT: modified intention-to-treat; N: total number; SD: standard deviation

Note: Odds ratio is the odds of the treatment group attaining the endpoint over the odds in the placebo group.

Note: Pair-wise comparisons (2-sided p-values) for each treatment group versus placebo are based on a logistic regression model with proportion of patients with HbA_{1c} < 7% at LOCF Endpoint as the outcome variable, and treatment, baseline HbA_{1c} (%) and sulfonylureas stratification based on randomization as explanatory variables. The p-value for a particular treatment group can only be assessed for significance if the change from baseline HbA_{1c} and the change in body weight at the LOCF Endpoint are both significant at alpha = 0.025 for that treatment group comparison.

6.2 Phase 3 Study 103 (High Baseline Sub-Study)

6.2.1 Study Design

6.2.1.1 Overview

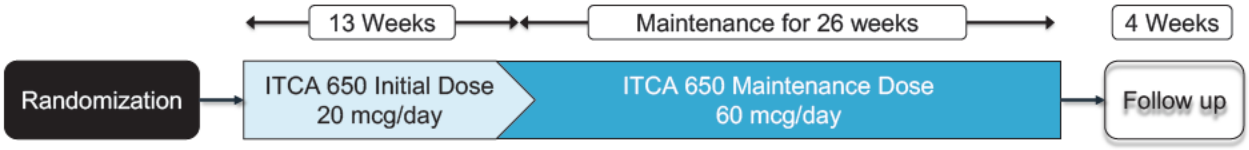
When enrolling Study 103 above, it was considered clinically inappropriate to include patients with high baseline HbA_{1c} levels (> 10%) in a placebo-controlled study. Thus, a portion of patients who were eligible for Study 103 except for high baseline levels of HbA_{1c} were eligible to receive open-label treatment with ITCA 650 in Study 103 HBL for up to 39 weeks. Patients who completed this study were eligible to receive continued treatment with ITCA 650 by participating in optional extension periods of 26 weeks, each of which went on for nearly 5 years. Study 103 HBL and its extensions also provided for long-term- evaluation of safety and persistence of efficacy, albeit uncontrolled, of the proposed ITCA 650 dosing regimen in the target patient population.

Study 103 HBL was a US-only open-label, single-arm, Phase 3 sub-study designed to evaluate the efficacy, safety, and tolerability of ITCA 650 for up to 39 weeks in patients with a high baseline HbA_{1c} (> 10% and ≤ 12%).

The eligible patient population in the Phase 3 Study 103 HBL was the same as the pivotal Study 103 except patients had poorly controlled, high HbA_{1c} levels at baseline (defined as HbA_{1c} > 10% and ≤ 12%) despite stable regimens of diet, exercise, and optimal or near-optimal regimens of background oral anti-diabetic medications. This single-arm, open-label study was designed with the purpose of evaluating treatment with ITCA 650 in adults with T2DM who represent a diabetes subpopulation whose hyperglycemia is generally more difficult to control.

The core sub study consisted of 3 periods: a 4-week screening period; a 39-week treatment period that included a 13-week period with an introductory dose of 20 mcg/day followed by a 26-week period of 60 mcg/day; and a 4-week safety follow-up period (Figure 14). Patients who completed the 39-week treatment period of this sub-study were eligible to receive continued open-label ITCA 650 by participating in optional extensions of up to 26 weeks and up to 1 year. Patients who continued into the extension phases did so without interruption in drug administration and did not complete the 4-week follow-up visit until after completing treatment.

Figure 14: Study 103 High Baseline Sub-Study Design



Primary Endpoint:

- The change in HbA_{1c} between baseline and Week 39.

  The LOCF Endpoint was defined as the last non-missing, on-treatment observation measured after baseline and before taking rescue medication. If non-missing, the LOCF Endpoint was 39 weeks. Patients who took rescue therapy were included with their last post-baseline HbA_{1c} value before beginning rescue therapy carried forward. This methodology was used for all endpoints in the sub-study.

Key Secondary Endpoints:

- Change in body weight between baseline and LOCF Endpoint.
- The proportion of patients with $HbA_{1c} < 7\%$ at Week 39.
- Changes from baseline in fasting plasma glucose (FPG), lipids (TC, TG, LDL-C, HDL-C, ApoB-100), biomarkers (hsCRP, adiponectin, HOMA-IR, HOMA-β), and blood pressure at LOCF Endpoint.
- The number and percent of patients who took rescue medication and the time to first rescue during the treatment period were summarized. Additionally, the incidence of rescue medication was summarized by stable diabetes regimen (diet and exercise alone, diet and exercise in combination with medications).

6.2.2 Patient Population

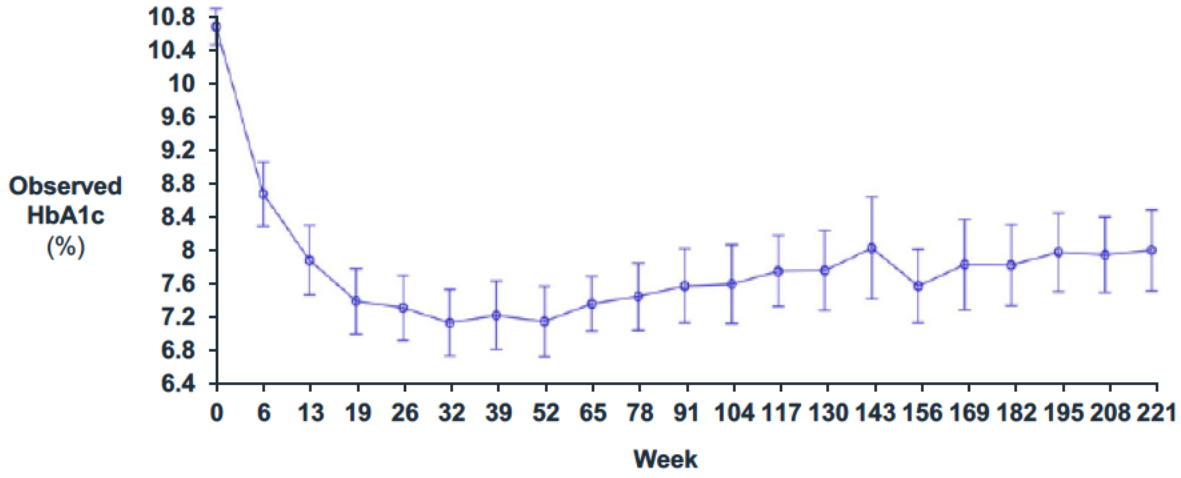
The higher percentage of patients requiring rescue compared to the pivotal studies is not unexpected given similar rescue criteria as the pivotal trials while having a significantly higher baseline HbA_{1c} (> 10–12%). The majority (42/60 [70%]) of sub-study patients were taking one or more background anti-diabetic medications and other concomitant medications.

6.2.3 Primary and Secondary Efficacy Results

The study met its primary objective by demonstrating a statistically significant reduction from baseline HbA_{1c} at the Week 39 endpoint. Clinically meaningful reductions in HbA_{1c} were observed by Week 6 and were well maintained below baseline levels throughout the 39-week sub-study and up to 182 additional weeks (nearly 5 years in total) thereafter in patients with T2DM who had high baseline HbA_{1c} levels prior to ITCA 650 (Figure 15).

Results of the analyses on the primary endpoint and secondary endpoints are shown in Table 6.

Figure 15: Study 103 High Baseline Sub-Study Mean (±2 SE) Change from Baseline HbA_{1c} (%) to Week 221 (mITT Population)



Note: The error bars represent the average measurement plus and minus 2 times the standard error.
Note: Data represented by mITT populations for the sub-study and each extension: 59 patients (sub-study), 38 patients at 65 weeks (Ext 1), 31 patients (Ext 2), 28 patients (Ext 3), 26 patients (Ext 4) and 24 patients (Ext 5).

Table 6: Study 103 High Baseline Sub-study Summary of Primary and Secondary Endpoints (mITT Population)

Study	Mean (SD) change (95% CI) in HbA_{1c} (%) at LOCF Endpoint, excluding post- rescue	LS mean (SE) change (95% CI) in HbA_{1c} (%) (MMRM), including post-rescue	Mean (SD) change (95% CI) in Body weight (kg) at LOCF Endpoint, excluding post-rescue	LS mean (SE) change (95% CI) in Body Weight (kg) (MMRM), including post- rescue	Percentage of Patients Treated to Target (HbA_{1c} < 7%) at LOCF Endpoint
Sub-study 39 weeks N = 59	-2.77% (1.416) (-3.14%, -2.41%) p < 0.001	-2.87 (0.166) (-3.20, -2.54) p < 0.001	-1.23 (5.746) (-2.73, 0.27) p = 0.105	-1.10 (0.646) (-2.38, 0.18) p = 0.092	25.4

FPG: fasting plasma glucose; HbA1c: glycosylated hemoglobin; MMRM: repeated measure analysis
Note: The LS Mean (SE), 95% CI, and p-value are from a fixed effects repeated measures ANCOVA model with the change in HbA1c as the outcome variable and baseline, visit, and baseline by visit interaction as explanatory variables. The correlation of the repeated measures is modeled with a first order autoregressive covariance structure. The p-value and CI for this sensitivity analysis are presented for descriptive purposes only.

Statistically and clinically significant decreases in FPG were also observed during the 39-week sub-study (mean decrease of -3.42 mmol/L [95% CI: (-4.46, -2.39); p < 0.001]) and up to 182 additional weeks of treatment with ITCA 650 60 mcg/day.

6.3 Pivotal Phase 3 Efficacy Study 105

6.3.1 Study Design

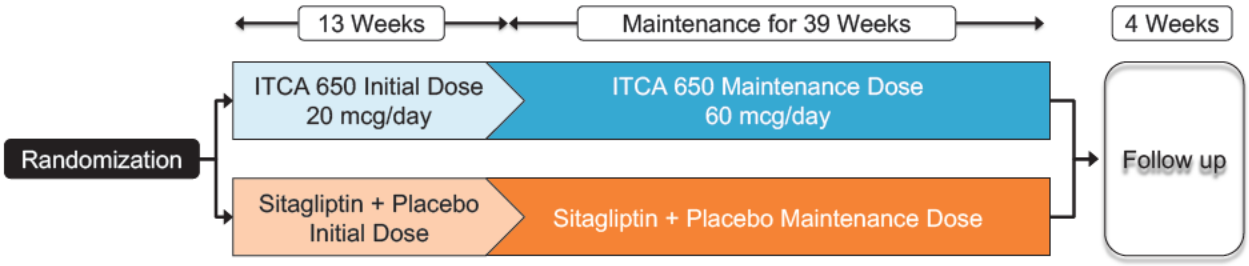
6.3.1.1 Overview

Study ITCA-650-CLP-105 (Study 105) was a pivotal, global, randomized, active comparator-, double-blind, double-dummy, head-to-head Phase 3 study to evaluate the efficacy, safety, and tolerability of ITCA 650 20/60 mcg/day compared with 100 mg/day oral sitagliptin (Januvia®) for up to 52 weeks. Since ITCA 650 was being developed as a maintenance therapy for patients known to not be adherent to daily or weekly medicines, Intarcia conducted this study to show the efficacy and safety of ITCA 650 vs. one of the most commonly prescribed oral medicines. The primary study objective was to determine whether ITCA 650 was non-inferior to sitagliptin in reducing HbA-$_{1c}$ in patients with T2DM following 52 weeks of treatment. Other secondary endpoints with the ability to test for superiority were also included.

Eligible patients included adults who had T2DM diagnosed ≥ 3 months prior to screening, had measured screening HbA_{1c} levels and between 7.5% and 10.5%, and were at a BMI between 25 to 45 kg/m^2, inclusive.

The study comprised 3 periods: a 4-week screening period; a 52 -week, double-blind, treatment period that included a 13-week period with an introductory dose of ITCA 650 20 mcg/day (or sitagliptin 100 mg/day) followed by 39 weeks with ITCA 650 60 mcg/day or sitagliptin 100 mg/day; and a 4-week safety follow-up- period (Figure 16).

Figure 16: Study 105 Study Design



Primary Endpoint:

- Change from baseline in HbA_{1c} (%) between Week 52 and Day 0 (testing for non-inferiority)

Secondary Endpoints:

- Change from baseline in HbA_{1c} (%) between Week 52 and Day 0 (testing for superiority)

- Composite HbA_{1c}/weight reduction through Week 52, defined as proportion of patients who experienced a decrease from baseline HbA_{1c} of > 0.5% and weight loss of ≥ 2 kg between Week 52 and Day 0
- Change in body weight between Week 52 and Day 0
- Proportion of patients with HbA_{1c} < 7% at Week 52

6.3.2 Patient Population

Demographics, baseline characteristics, diabetes history, and medical history were similar across the treatment groups. The reported medical history events were generally characteristic of what would be expected for patients with T2DM within the age range of the study patients, with 66.4% having hypertension, and 22.1%, 16%, and 14.5% reporting hyperlipidemia, dyslipidemia, and hypercholesterolemia, respectively.

All patients were on biguanides as metformin use was an inclusion criterion. There were no notable differences in background metformin use at screening or baseline between the two treatment groups. Similar percentages of patients in the 2 groups increased metformin dose prior to randomization (49/265 [18.5%] ITCA 650 20/60 mcg/day and 53/265 [20.0%] sitagliptin).

All patients reported the use of concomitant medications, which were generally similar between the two treatment groups and consistent with the disease state. A notable difference was the more frequent use of SUs and long-acting insulins and analogues by patients in the sitagliptin treatment group (~6–9% ITCA 650 vs ~17–18% sitagliptin), reflecting the greater use of rescue therapy in this group.

6.3.3 Primary Efficacy Results

Results of the primary analysis established non-inferiority of ITCA 650 compared with sitagliptin. Following 13 weeks of treatment with ITCA 650 20 mcg/day followed by 39 weeks of treatment with ITCA 650 60 mcg/day, the difference between the two groups at Week 52 was -0.71%, with corresponding 2-sided 95% CI of (-0.93%, -0.49%; p < 0.001' Table 7). These results were both clinically and statistically significant.

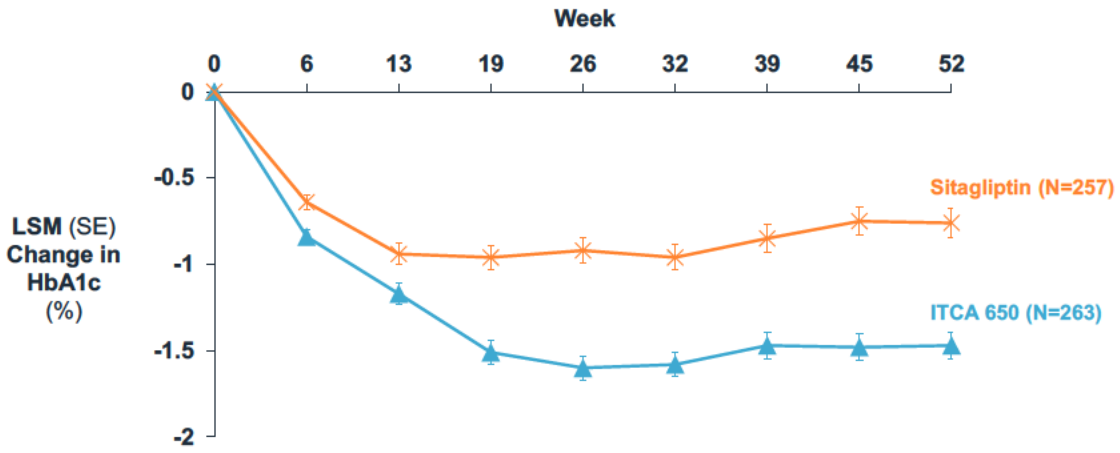
As shown in Figure 17, although decreases from baseline were observed for both groups, reductions in HbA_{1c} were numerically greater with ITCA 650 compared with sitagliptin by Week 6, continued to decrease through Week 26 following an increase in ITCA 650 dose, and were well maintained with the 6-month maintenance implant for the remaining treatment period.

Table 7: Study 105 Statistical Analyses on Change from Baseline HbA1c (%) at Week 52

Analysis Model and Population	HbA_{1c} LS Mean and LS Mean Difference at Week 52	
	ITCA 650 20/60 mcg/day (N = 263)	Sitagliptin 100 mg/day (N = 257)
Baseline HbA_{1c} (%)		
Mean (SD)	8.54 (0.929)	8.65 (0.905)
Median (Min, Max)	8.30 (6.4, 11.4)	8.50 (6.8, 10.8)
Repeated Measures ANCOVA Analysis (mITT Population): pre-specified primary analysis[a]		
N	263	257
LS Mean (SE)	-1.47 (0.077)	-0.76 (0.082)
LS Mean Difference, 95% CI	-0.71 (-0.93, -0.49)	
p-value (vs sitagliptin)	< 0.001	

ANCOVA: analysis of covariance; CI: confidence interval; HbA_{1c}: glycosylated hemoglobin; LS: least-squares; mITT: modified intention-to-treat; n: number of patients included in the analysis calculation (depended on analysis method); N: total number; SD: standard deviation; SE: standard error
Note: LS mean difference = LS mean active treatment – LS mean sitagliptin.
Note: Baseline is defined as the last assessment on or before the day of the initial placement procedure of ITCA 650/placebo.
[a] The comparison (2-sided p-value) of ITCA 650 versus sitagliptin is based on LS means from a repeated measures model with each post-baseline visit treated as equally spaced repeated measures and an unstructured matrix describing the covariance between measurements taken at different visits. Treatment, visit, and the interaction between treatment and visit are included as fixed effects and baseline HbA_{1c} as the covariate. As the primary analysis, if the upper bound of the 95% CI of the LS Mean difference is less than the 0.3% margin, then ITCA 650 is non-inferior to sitagliptin. Furthermore, as a secondary analysis, if the upper bound of the 95% CI is less than 0, then ITCA 650 is superior to sitagliptin.

Figure 17: Study 105 LS Mean Change (± 2 SE) from Baseline HbA1c During the Treatment Period with ITCA 650 20/60 mcg/day Regimen vs Sitagliptin 100 mg/day (mITT Population)



HbA_{1c}: glycosylated hemoglobin; LS: least-squares; mITT: modified intention-to-treat; PBO: placebo; SE: standard error.
Note: The error bars represent the least-squares mean of change from baseline HbA_{1c} (%) plus and minus 2 times the SE based on a repeated measures model with baseline and each post-baseline visits treated as equally spaced repeated measures and an unstructured matrix describing the covariance between measurements taken at different visits. Treatment, visit, and the interaction between treatment and visit are included as fixed effects. The 2-sided p-values for comparing ITCA 650 with sitagliptin are presented per visit for descriptive purposes only.

6.3.4 Secondary Efficacy Results

As the upper bound of the 2-sided 95% CI for the LS mean difference between ITCA 650 and sitagliptin at Week 52 was < 0, superiority of ITCA 650 to sitagliptin was established (Table 7).

Results were consistent with the demonstration of superiority of ITCA 650 to sitagliptin in terms of change in HbA_{1c} to Week 52 in a secondary analysis for the composite HbA_{1c}/weight reduction. The proportion of patients achieving a composite HbA_{1c}/weight reduction at Week 52 was greater in the ITCA 650 group than sitagliptin group (60.8% [104/171] vs 27.8% [35/126], respectively); the analysis was conducted for patients with measurements at Week 52 with no imputations. The odds of achieving the composite endpoint with ITCA 650 was 3.6-fold greater than with sitagliptin, which was statistically significant [95% CI: (2.333, 5.642); p < 0.001]. When early terminated and rescued patients were treated as non-responders across Study 103 and Study 105 for the 20/60 mcg/day groups, results remained consistent.

The mean change in body weight from baseline to Week 52 in the ITCA 650 group was statistically significantly greater in the ITCA 650 group than sitagliptin group (p < 0.001; Table 8). The difference between the two treatment groups was significant at all post-baseline assessments. Incremental weight loss was notable with ITCA 650 after dose escalation at Week 13.

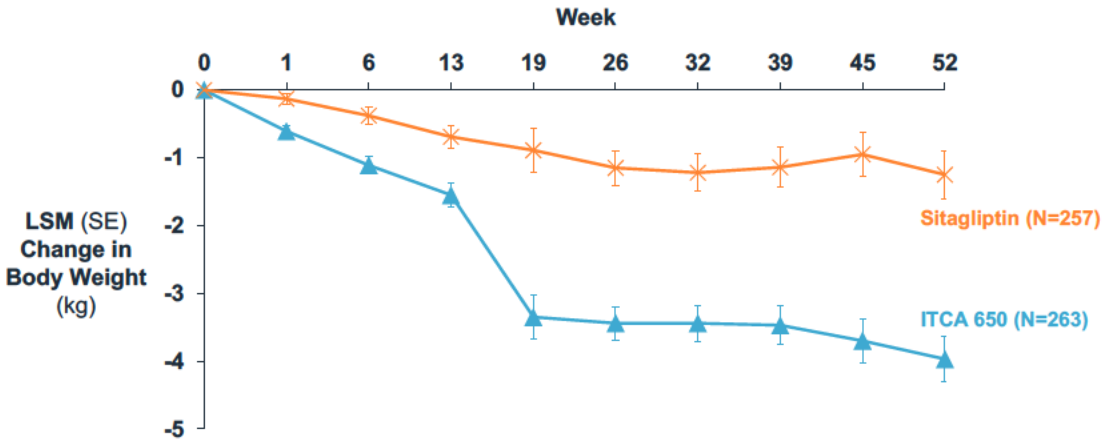
Table 8: Study 105 Statistical Analyses on Change from Baseline Body Weight at Week 52

Analysis Model and Population	Body Weight (kg) LS Mean and Difference at Week 52	
	ITCA 650 20/60 mcg/day (N = 263)	Sitagliptin 100 mg/day (N = 257)
Baseline Body Weight (kg)		
Mean (SD)	92.19 (19.917)	92.03 (21.369)
Median (Min, Max)	89.80 (54.6, 158.9)	89.90 (55.6, 176.0)
Repeated Measures Analysis (mITT Population), post-rescue excluded: pre-specified primary analysis[a]		
N	263	257
LS Mean (SE)	-3.97 (0.330)	-1.25 (0.350)
LS Mean Difference, 95% CI	-2.71, (-3.66, -1.77)	
p-value (vs sitagliptin)	< 0.001	

CI: confidence interval; LS: least-squares; mITT: modified intention-to-treat; n: number of patients included in the analysis calculation (depended on analysis method); N: total number; SE: standard error
Note: LS mean difference = LS mean active treatment – LS mean placebo.
Note: Baseline is defined as the last assessment on or before the day of the initial placement procedure of ITCA 650/placebo.

[a] The comparison (2-sided p-value) of ITCA 650 versus sitagliptin is based on LS means from a repeated measures model with each post-baseline visit treated as equally spaced repeated measures and an unstructured matrix describing the covariance between measurements taken at different visits. Treatment, visit, and the interaction between treatment and visit are included as fixed effects and baseline body weight as the covariate. The p-value for this endpoint could only be assessed for significance (per Hochberg's multiple test procedure specified in the SAP), if the superiority of ITCA 650 to sitagliptin in the composite HbA_{1c}/weight reduction endpoint was significant at the $\alpha = 0.05$ level.

Figure 18: Study 105 LS Mean (± 2 SE) Change from Baseline Body Weight During the Treatment Period with ITCA 650 20/60 mcg/day Regimen vs Sitagliptin 100 mg/day (mITT Population)



mITT: modified intention-to-treat; PBO: placebo; SE: standard error

Note: The error bars represent the least-squares mean body weight (kg) plus and minus 2 times the SE based on a repeated measures model with baseline and each post-baseline visits treated as equally spaced repeated measures and an unstructured matrix describing the covariance between measurements taken at different visits. Treatment, visit and the interaction between treatment and visit are included as fixed effects. Two-sided p-values for comparing ITCA 650 with sitagliptin are presented per visit for descriptive purpose only.

A significantly higher proportion of patients in the mITT population achieved $HbA_{1c} < 7\%$ at Week 52 in the ITCA 650 group than in the sitagliptin treatment group (60.8% [104/171] vs 42.1% [53/126], respectively; $p < 0.001$); The analysis included only patients with measurements at Week 52 with no imputation. The odds ratio between the two groups was 2.955 [95% CI: (1.975, 4.541); $p < 0.001$].

6.4 Cardiovascular Outcomes Trial 107 (Study 107)

6.4.1 Study Design

6.4.1.1 Overview

Study 107 in 4,156 patients was a Phase 3 randomized, double-blind, placebo -controlled, event-based pre-approval CVOT conducted across 402 active global sites (defined as sites having randomized at least one patient). The target population for this study consisted of patients with an increased risk for CV events who may have benefited from additional antidiabetic treatment. This population consisted of 2 subgroups: high-risk and low-risk. The high risk- group consisted of patients at least 40 years of age with a diagnosis of T2DM and a history of at least 1 documented occurrence of coronary artery disease (CAD). The low-risk group were patients who

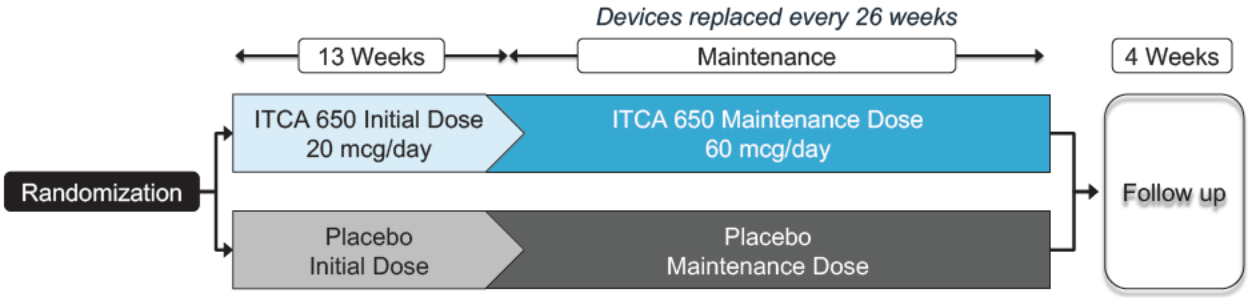
were at least 60 years of age with at least 1 other risk factor in addition to T2DM. Enrollment in the low-risk population was limited to 25% of the study population. All patients were required to have an $HbA_{1c} \geq 6.5\%$ at Screening.

The primary objective was to obtain CV outcome event data in an enriched population with T2DM and high CV risk. For the primary endpoint these data were pooled with CV event data from the other Phase 3 pivotal studies (Study 103 and Study 105) in a prospectively defined Phase 3 program meta-analysis to determine whether the upper limit of the 95% CI of the hazard ratio of first occurrence of MACE (non-fatal myocardial infarction [MI], non-fatal stroke, CV death, hospitalization for UA) in adult patients with T2DM on standard of care therapy receiving either ITCA 650 or ITCA placebo was < 1.8.

Efficacy endpoints collected in this study were exploratory and included changes in HbA_{1c} and body weight, and the proportion of patients achieving $HbA_{1c} < 7\%$. While these efficacy endpoints were exploratory, results from this study provided a significant source of unbiased data supporting the use of ITCA 650 as an adjunct treatment in adults with T2DM.

The event driven trial consisted of four periods: a 4-week screening period, a 13-week introductory dose period (ITCA 650 20 mcg/day or ITCA 650 placebo), and a treatment maintenance period with ITCA 650 60 mcg/day or ITCA 650 placebo with devices replaced every 26 weeks or 6 months, and a 4-week follow-up- period (Figure 19).

Figure 19: Study 107 Study Design



Primary Safety Endpoint:

- Time to first occurrence of any event in the major adverse cardiovascular event composite endpoint (CV death, non-fatal MI, non-fatal stroke, or hospitalization for UA)

Efficacy endpoints were pre-specified but not multiplicity adjusted.

Changes in baseline HbA_{1c}, FPG, body weight, blood lipids (total cholesterol, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol),

blood pressure (systolic and diastolic), and albumin/creatinine ratio between baseline and Month 3, Month 9, and every 6 months of treatment thereafter were evaluated. Additionally, the changes in each of these parameters to the last on-treatment visit, the last study period assessment (on or off treatment), and each post-treatment visit were also determined.

Additional efficacy endpoints included the following:

- The proportions of patients achieving a target HbA_{1c} < 7% and < 6.5% at Month 9, Month 15, and every 6 months thereafter were determined, as well as the proportions at these two HbA_{1c} targets at the last on-treatment visit and for the last result during the study period (on or off treatment).
- Time to intensification of therapy (defined as the addition of any new anti-diabetic rescue medication) and time to a new insulin therapy. [Note that changes involving additions of new anti-diabetic therapies were captured but dose adjustments in current anti-diabetic treatments were not assessed.]

Additional information regarding the design of Study 107 is provided in Appendix Section 13.1.

6.4.2 Patient Population

Detailed information on the patient population in Study 107 is provided in Appendix Section 13.2.3.

A total of 4,156 patients were randomized and comprised the ITT population, including 2,075 patients in the ITCA 650 20/60 mcg/day group and 2,081 patients in the ITCA placebo group. A total of 653 patients discontinued during the trial, including 365 patients (17.6%) in the ITCA 650 group and 288 patients (13.8%) in the placebo group.

In Study 107, demographic baseline characteristics, diabetes history, and notable medical history were similar between the 2 treatment groups. The reported medical history was comparable across the treatment groups and generally characteristic of what would be expected for patients with T2DM and CV disease or risk factors within the age range of the study population.

More than half of all patients were using statins, aspirin, non-aspirin anti-platelets, and other anti-hypertensive medications at baseline. The proportion of patients using SUs and long-acting insulins and analogues was higher in the ITCA placebo treatment group, reflecting a greater likelihood of adding an antidiabetic medication after baseline. Medications for treating GI conditions (proton pump inhibitors and serotonin antagonists) were more commonly used by patients in the ITCA 650 group than placebo group (21.6% vs 17.1%, respectively, and 7.8% vs 1.9%, respectively).

Like in other CVOTs, the patient population was at a higher risk of AKI due to known risk factors related to underlying renal impairment at baseline (70%), and use of concomitant medications known to increase the risk of dehydration and AKI.

Specifically, > 85% of patients in the trial were on metformin (GI AEs common), over 75% were on an ARBs/ACE inhibitors, and 28% were on one or more diuretics. Non-steroidal anti-inflammatory drugs (NSAIDs) were also commonly used.

6.4.3 Efficacy Results

The primary safety analyses of this study are presented in Section 7.8.3.1.

All efficacy analyses were exploratory; results described as significant refer to an exploratory p-value of < 0.05. Results of the analyses on HbA_{1c} and body weight by treatment group and visit are summarized in Table 9.

Table 9: Study 107 Summary of Key Exploratory Efficacy Analyses: Change from Baseline HbA1c (%) and Body Weight to Last Available on Treatment and Last Available Value (mITT-2 Population)

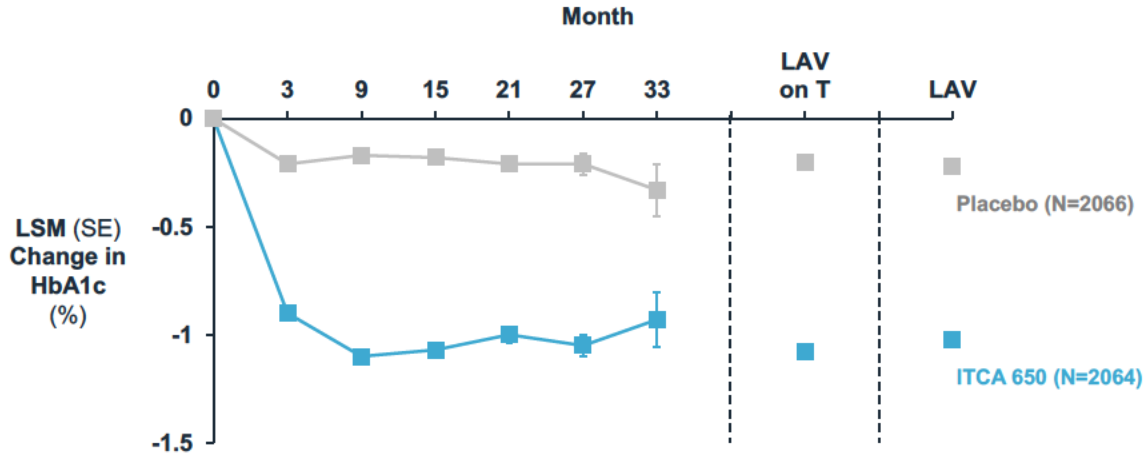
		HbA_{1c} (%)		Body Weight (kg)	
Visit	**Statistic**	**ITCA 650 20/60 mcg/d**	**Placebo**	**ITCA 650 20/60 mcg/d**	**Placebo**
Baseline	**n**	2064	2066	2063	2066
	Mean (SD)	8.37 (1.505)	8.35 (1.515)	93.96 (19.236)	93.64 (19.918)
	Median (Min, Max)	8.00 (5.3, 14.5)	8.00 (5.2, 15.4)	92.00 (41.5, 197.5)	91.00 (39.0, 190.1)
Last Available Value On-Treatment	**n**	2050	2061	2055	2062
	LS Mean (SE)	-1.08 (0.029)	-0.20 (0.029)	-4.37 (0.143)	-0.86 (0.143)
	LS Mean Difference	-0.88		-3.51	
	95% CI of LS Mean Difference	(-0.95, -0.80)		(-3.87, -3.15)	
	p-value	< 0.001		< 0.001	
Last Available Value	**n**	2064	2066	2063	2065
	LS Mean (SE)	-1.02 (0.029)	-0.22 (0.029)	-3.54 (0.148)	-0.70 (0.148)
	LS Mean Difference	-0.80		-2.84	
	95% CI of LS Mean Difference	(-0.87, -0.72)		(-3.22, -2.46)	
	p-value	< 0.001		< 0.001	

HbA_{1c}: glycosylated hemoglobin; LS: least-squares; mITT-1: first modified intention-to-treat population that included all randomized patients who had a procedure started for the initial ITCA 650/placebo placement; mITT-2: second modified intention-to-treat population that included all patients in mITT-1 population who had a valid baseline and at least one post-baseline HbA_{1c} value; n: number of patients included in the analysis calculation (depended on analysis method); SD: standard deviation; SE: standard error
Note: Baseline is defined as the last assessment on or before the day of the initial placement procedure of ITCA 650/Placebo.

Clinically relevant decreases in HbA1c in the ITCA 650 20/60 mcg/day group were apparent within the first 3 months of treatment and well maintained for up to 33 months (Figure 20). In contrast, mean HbA1c remained relatively close to baseline levels for

patients in the ITCA placebo treatment group. The difference between treatment groups was maintained to the last available on-treatment value and the last available value (both $p < 0.001$).

Figure 20: Study 107 Line Graph of Least-Square Mean (± 2 SE) of Change from Baseline HbA1c (%) by Visit (mITT-2 Population)

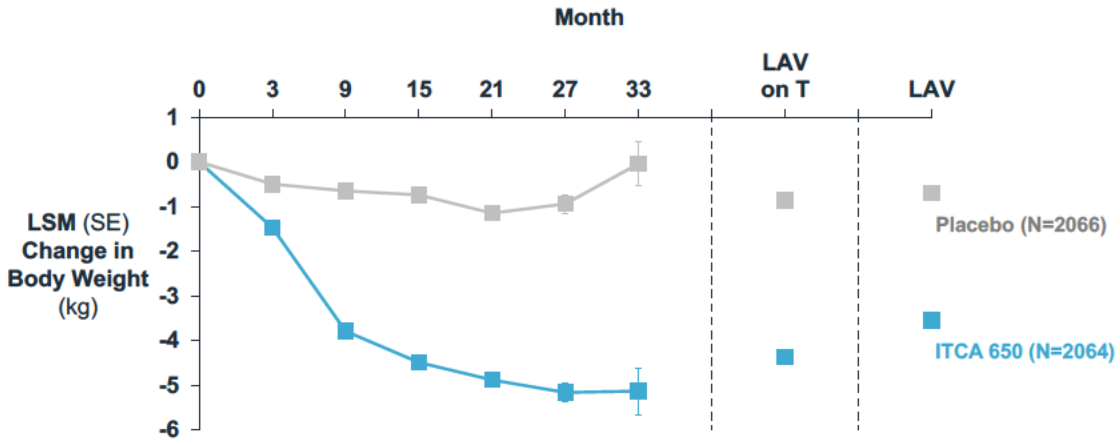


HbA_{1c}: glycosylated hemoglobin; LAV: last available value; LAV on T: last available value on treatment; LS: least-squares; mITT-1: first modified intention-to-treat population that included all randomized patients who had a procedure started for the initial ITCA 650/placebo placement; mITT-2: second modified intention-to-treat population that included all patients in mITT-1 population who had a valid baseline and at least one post-baseline HbA_{1c} value; PBO: placebo; SE: standard error

Across all subgroups analyzed, decreases in HbA_{1c} and body weight from baseline to the last on-treatment assessment for the ITCA 650 group were of greater magnitude compared with responses for the ITCA placebo group.

Within the first 3 months of treatment, decreases in body weight from baseline were observed with ITCA 650 20/60 mcg/day that were well maintained through 33 months as shown in Figure 21. In contrast, body weight remained relatively stable in the placebo group. The difference between treatment groups increased during the study to the last available on-treatment value and the last available value (both $p < 0.001$). Overall, the results for both treatment groups in the subgroups analyzed were consistent with results of the main exploratory analysis of body weight by visit. However, there was a trend for decreases in body weight to be greater in the subgroup with baseline BMI ≥ 30 kg/m^2 compared with the subgroup with baseline BMI < 30 kg/m^2.

Figure 21: Study 107 LS Mean (± 2 SE) of Change from Baseline Body Weight by Visit (mITT-2 Population)



LAV: last available value; LAV on T: last available value on treatment; LS mean: least-square mean; mITT-1: first modified intention-to-treat population that included all randomized patients who had a procedure started for the initial ITCA 650/placebo placement; mITT-2: second modified intention-to-treat population that included all patients in mITT-1 population who had a valid baseline and at least one post-baseline HbA_{1c} value; SE: standard error

6.5 Efficacy Conclusions

All ITCA 650 randomized, controlled, studies met their key pre-specified clinical endpoints.

In accordance with FDA and European Medicines Agency (EMA) guidance, change from baseline in HbA_{1c} was the primary efficacy endpoint in the Phase 3 pivotal efficacy studies evaluating the efficacy of ITCA 650. Other relevant efficacy endpoints included change from baseline in body weight and percentage of patients treated to HbA_{1c} targets of < 7%.

Treatment with ITCA 650 20/60 mcg/day resulted in statistically superior and clinically significant improvements in HbA_{1c} compared to placebo and to sitagliptin 100 mg/day.

Significant reductions in HbA_{1c} were evident within the first 6 weeks of treatment with the initiation dose of ITCA 650 20 mcg/day. HbA_{1c} continued to decrease following escalation to the maintenance dose of 60 mcg/day, reaching a nadir at approximately 26–32 weeks that was well maintained for chronic treatment periods, including for > 200 weeks in an open-label extension study of patients with T2DM with high baseline HbA_{1c} values.

Significant reductions in body weight were observed within the first 6 weeks of treatment with ITCA 650 20 mcg/day. Body weight progressively decreased after dose escalation to 60 mcg/day, resulting in statistically significant reductions from baseline to Week 39 and Week 52 that were greater compared to ITCA placebo and to sitagliptin, respectively.

7 CLINICAL SAFETY

Summary

- The incidence and types of AEs observed with ITCA 650 are in-line with the well-established safety profile of exenatide and approved GLP-1s which include class-labeled AKI Warnings that are associated with GI AEs.
- Like all GLP-1s, GI AEs are the most common AEs for ITCA 650. Transient nausea, vomiting, or diarrhea were observed during dose initiation and dose escalation; thereafter, GI AEs decline to low levels (< 2%) (Figure 22).
  - > 97% of GI AEs reported on ITCA 650 were mild to moderate, and GI AE discontinuation rates were 8%, in-line with approved GLP-1 products.
- A small numeric imbalance in treatment-emergent AKI SAEs (11 [0.5%] for ITCA 650 vs 4 [0.2%] for placebo) was observed in the CVOT, Study 107.
  - All 11 ITCA-650 patients had multiple background risk factors for AKI that are known and labeled for the GLP-1 class.
  - All AKI events on ITCA 650 resolved, and 6 of 11 patients remained on ITCA 650 and successfully finished the trial.
  - No AKI deaths occurred on drug vs 2 on placebo, and there was no increase in dialysis.
- Serious AKI events associated with GI AEs (a Warning and class effect) are a risk that is not isolated to ITCA 650 in RCTs or post-marketing events; the risk exists for all GLP-1s and can be effectively labeled, monitored, and mitigated.
  - USPIs for all GLP-1 products carry AKI Warnings that emphasize the known association with GI AEs that must be monitored and mitigated.
  - Additional risk factors include underlying renal impairment and use of concomitant medications that impact hydration status and renal function.
  - Warnings also focus on monitoring renal function in renal impaired patients with early-on GI AEs, informing patients about a risk of AKI with dehydration, and instructions to avoid dehydration and report any issues.
- The primary safety (MACE) endpoint was met in CVOT Study 107 and meta-analysis, satisfying the 2008 FDA guidance requirements with the upper bound of 95% CI for HR < 1.8 when comparing CV events for ITCA 650 vs control.
- A more definitive (larger, properly powered, and longer-duration) CVOT needs to be conducted post-approval (Section 9.1).

7.1 Safety Populations and Treatment Exposure ITCA 650 20/60 mcg/day PS2 Pool

The safety of ITCA 650 has been thoroughly evaluated through the Pooled Safety Population, which includes patients from Studies 103, 105, and 107. The Pooled Safety Population comprises:

- 2,488 patients who received ITCA 650 20/60 mcg/day
- 2,228 patients who received placebo

Cumulative exposure for the Pooled Safety Population is presented in Table 10.

Table 10: Treatment Exposure ITCA 650 20/60 mcg/day (Pooled Safety Population)

	Pooled ITCA 650 20/60 mcg N = 2,488	Pooled Placebo N = 2,228
Duration of Exposure (Weeks)		
Mean (SD)	13.54 (6.90)	14.43 (6.79)
Median (min, max)	12.02 (0.00, 31.54)	13.26 (0.03, 31.74)
Duration categories, n (%)		
< 1 Month	51 (2.0)	14 (0.6)
1–< 3 Months	43 (1.7)	33 (1.5)
3–< 6 Months	178 (7.2)	67 (3.0)
6–< 9 Months	501 (20.1)	512 (23.0)
9–< 12 Months	465 (18.7)	386 (17.3)
12–< 15 Months	373 (15.0)	299 (13.4)
15–< 18 Months	156 (6.3)	190 (8.5)
18–< 21 Months	306 (12.3)	293 (13.2)
21–< 27 Months	359 (14.4)	369 (16.6)
≥ 27 Months	56 (2.3)	65 (2.9)

SD: standard deviation

7.2 Overall Safety - ITCA 650 20/60 mcg/day

ITCA 650 was generally well tolerated with a safety profile that was consistent with the GLP-1 RA drug class.

The incidence of patients in the Pooled Safety Population with at least one TEAE during the treatment period was greater in the ITCA 650 group than in the ITCA placebo group (Table 11). The imbalance was principally due to the increased incidence of transient GI AEs such as nausea and vomiting, further described in Section 7.8.1. TEAEs were mostly mild or moderate in severity and, aside from the GI events, occurred with similar

incidences between the ITCA 650 and ITCA placebo groups. Severe TEAEs occurred with a similar incidence between the ITCA 650 and ITCA placebo groups.

The incidence of patients with serious TEAEs and TEAEs leading to death were similar between the ITCA 650 and placebo treatment groups. There were no treatment emergent- serious AKI related deaths in the ITCA 650 group; all patients recovered. Two of the 4 serious AKIs on placebo resulted in deaths.

TEAEs leading to permanent discontinuation of study medication were more common in the ITCA 650 group than in the placebo group.

Table 11: Overall Summary of Treatment-Emergent Adverse Events During the Treatment Period (Pooled Safety Population)

	Pooled ITCA 650 20/60 mcg/day N = 2,488 n (%)	Pooled Placebo N = 2,228 n (%)
Any TEAE	1,839 (73.9)	1,435 (64.4)
TEAEs by severity		
Mild	718 (28.9)	586 (26.3)
Moderate	834 (33.5)	638 (28.6)
Severe	287 (11.5)	211 (9.5)
SAEs	356 (14.3)	303 (13.6)
AEs leading to permanent discontinuation of study medication	304 (12.2)	106 (4.8)
AEs leading to death	46 (1.8)	35 (1.6)

AE: adverse event; SAEs: serious adverse events; TEAE: treatment-emergent adverse event

7.3 Common Adverse Events

In the ITCA 650 treatment group, the System Organ Class (SOC) with the greatest incidence TEAEs and that occurred more frequently compared with the ITCA placebo treatment group, was the GI disorders SOC. As expected for exenatide and GLP-1s, the most common GI TEAEs were nausea, vomiting, and diarrhea during dose initiation and dose escalation in a sub-set of patients (Table 12). Like all GLP-1 products, these events were transient in nature and declined after dose escalation (Figure 6).

These events are a known AE with all approved GLP-1 products and are listed within current exenatide and GLP-1 labeling. Thus, patients, in particular those with known/labeled underlying AKI risk factors, will be proactively monitored and informed of the risk and of the need to remain hydrated and monitor renal function if these transient events occur during the two dosing windows early-on. GI events are further described in Section 7.8.1.

Table 12: Incidence of Patients with Treatment-Emergent Adverse Events ≥ 2% During the Treatment Period (Pooled Safety Population)

Preferred Term	Pooled ITCA 650 20/60 mcg/day N = 2,488 n (%)	Pooled Placebo N = 2,228 n (%)
Any TEAE	1,429 (57.4)	926 (41.6)
Nausea	557 (22.4)	90 (4.0)
Vomiting	367 (14.8)	27 (1.2)
Hypoglycemia*	223 (9.0)	96 (4.3)
Diarrhea	210 (8.4)	88 (3.9)
Urinary tract infection	145 (5.8)	112 (5.0)
Device difficult to use	112 (4.5)	99 (4.4)
Lipase increased	106 (4.3)	38 (1.7)
Dyspepsia	97 (3.9)	24 (1.1)
Constipation	89 (3.6)	20 (0.9)
Decreased appetite	87 (3.5)	8 (0.4)
Upper respiratory tract infection	83 (3.3)	81 (3.6)
Bronchitis	61 (2.5)	58 (2.6)
Hyperglycemia	61 (2.5)	99 (4.4)
Nasopharyngitis	54 (2.2)	46 (2.1)

TEAE: treatment-emergent adverse event
*0% of patients experienced hypoglycemia in absence of insulin and SU con-meds. Pooled Safety includes Studies 103, 105, 107

7.4 Adverse Events Grade ≥ 3

Severe TEAEs also occurred at a similar incidence between the ITCA 650 and ITCA placebo groups (Table 13).

The SOC with the greatest incidence of severe TEAEs, and that was greater in the ITCA treatment group compared with ITCA placebo, was GI disorders. Again, this difference was driven by the most common transient TEAEs of nausea, vomiting, and diarrhea.

Table 13: Adverse Events Grade ≥ 3 (> 5 Patients, Pooled Safety Population)

Preferred Term	Pooled ITCA 650 20/60 mcg/day N = 2,488 n (%)	Pooled Placebo N = 2,228 n (%)
Any severe AE	287 (11.5)	211 (9.5)
Nausea	39 (1.6)	3 (0.1)
Vomiting	29 (1.2)	3 (0.1)
Acute myocardial infarction	13 (0.5)	8 (0.4)
Pneumonia	8 (0.3)	6 (0.3)
Acute kidney injury	8 (0.3)	3 (0.1)
Angina pectoris	8 (0.3)	3 (0.1)
Coronary artery disease	7 (0.3)	9 (0.4)
Hypoglycemia	7 (0.3)	5 (0.2)
Cardiac failure	7 (0.3)	3 (0.1)
Atrial fibrillation	7 (0.3)	2 (< 0.1)
Acute coronary syndrome	6 (0.2)	3 (0.1)
Myocardial infarction	4 (0.2)	8 (0.4)
Angina unstable	3 (0.1)	7 (0.3)

AE: adverse event

7.5 Serious Adverse Events

The overall incidence of SAEs was similar between the ITCA 650 and placebo treatment groups (Table 14). Notably, none of the TEAEs within the GI disorders SOC had an incidence of > 2% in the ITCA 650 treatment group.

Table 14: Serious Adverse Events (Pooled Safety Population)

Preferred Term	Pooled ITCA 650 20/60 mcg/day N = 2,488 n (%)	Pooled Placebo N = 2,228 n (%)
Any serious TEAE	356 (14.3)	303 (13.6)
Atrial fibrillation	16 (0.6)	9 (0.4)
Acute myocardial infarction	16 (0.6)	13 (0.6)
Angina pectoris	17 (0.7)	9 (0.4)
Angina unstable	14 (0.6)	21 (0.9)
Coronary artery disease	12 (0.5)	18 (0.8)
Cardiac failure	12 (0.5)	10 (0.4)
Pneumonia	10 (0.4)	15 (0.7)
Myocardial infarction	8 (0.3)	11 (0.5)

TEAE: treatment-emergent adverse event

7.6 Adverse Events Leading to Discontinuation

The overall incidence of patients with TEAEs leading to permanent discontinuation of study medication was higher in the ITCA 650 treatment group than in the ITCA placebo treatment group. The most frequent TEAEs resulting in permanent discontinuation of study medication in the ITCA 650 treatment group compared with the ITCA placebo treatment group were nausea and vomiting. All of the events leading to permanent discontinuation of study medication were reported as mild or moderate. As noted, the discontinuation rate for GI AEs was 8%, which is in-line with exenatide and approved GLP-1 products on the market.

7.7 Deaths

The overall incidence of TEAEs leading to death was similarly low between the ITCA 650 treatment group and the ITCA placebo treatment group. In total, 81 patients experienced TEAEs leading to death in the Pooled Safety Population during the treatment period: 46 (1.8%) in Pooled ITCA 650 20/60 and 35 (1.6%) in the placebo group. There was one death in the sitagliptin treatment group (Acute coronary syndrome).

Only one TEAE leading to death (mucinous cystadenocarcinoma of pancreas), which occurred to a patient treated with ITCA 650, was assessed by the Investigator as related to the study medication. The patient died on Study Day 423.

Table 15 presents the incidence of TEAEs leading to death, which occurred in at least two patients in the ITCA 650 group.

Table 15: Incidence of Treatment-Emergent Adverse Events Leading to Death During the Treatment Period in ≥ 2 Patients in the ITCA 650 All Doses Treatment Group (Pooled Safety Population)

Preferred Term	Pooled ITCA 650 20/60 mcg/day N = 2,488 n (%)	Pooled Placebo N = 2,228 n (%)
Any TEAE Leading to Death	46 (1.8%)	35 (1.6%)
Death	8 (0.3%)	3 (0.1%)
Myocardial infarction	3 (0.1%)	2 (< 0.1%)
Sudden cardiac death	3 (0.1%)	2 (< 0.1%)
Acute coronary syndrome	2 (< 0.1%)	0 (0.0%)
Hemorrhagic stroke	2 (< 0.1%)	0
Pneumonia	2 (< 0.1%)	1 (< 0.1%)
Sudden death	2 (< 0.1%)	0

TEAE: treatment-emergent adverse event

7.8 Adverse Events of Special Interest

AESIs included GI AEs, hypoglycemia/hyperglycemia, AKI, and MACE. Full details on AKI and MACE are presented in Sections 0 and 8.3, respectively, as part of Clinical Issues 1 and 2.

7.8.1 Gastrointestinal Adverse Events (Nausea, Vomiting, Diarrhea)

The incidence rates of nausea, vomiting, and diarrhea were all higher in the ITCA 650 treatment group than in the ITCA 650 placebo group (Table 16).

Severe GI AEs among patients treated with ITCA 650 were observed infrequently.

Table 16: Overview of Gastrointestinal Adverse Events

Preferred Term	Pooled ITCA 650 20/60 mcg/day N = 2,488 n (%)	Pooled Placebo N = 2,228 n (%)
Any GI AE	960 (38.6)	316 (14.2)
Mild GI AE	484 (19.5)	206 (9.2)
Moderate GI AE	397 (16.0)	93 (4.2)
Severe GI AE	79 (3.2)	17 (0.8)
Serious GI AEs	36 (1.4)	23 (1.0)
GI AEs leading to discontinuation of study medication	203 (8.2)	19 (0.9)
GI AEs leading to death	0	0

GI AE: gastrointestinal adverse event

A head-to-head Phase 2 dose ranging study of ITCA 650 vs Byetta (only exenatide injections available at the time) showed significantly less GI AEs on ITCA 650 during dose initiation testing the same dose of exenatide delivery via injections vs ITCA 650 implants for 12 weeks (Figure 34). There was also slightly better glucose control. Additionally, while recognizing the limitations of cross-trial comparisons, the rate of GI AEs and GI AE discontinuation rates with ITCA 650 are similar to other available GLP-1 RA products – whether looking at the prescribing labels, CVOT publications or regulatory reviews (Table 20). Overall, the GI AEs vs. exenatide injections (Byetta) were favorable and there is no evidence of any clinically meaningful difference in published GI AEs for ITCA 650 vs. what is published in similar trials for numerous other GLP-1 products.

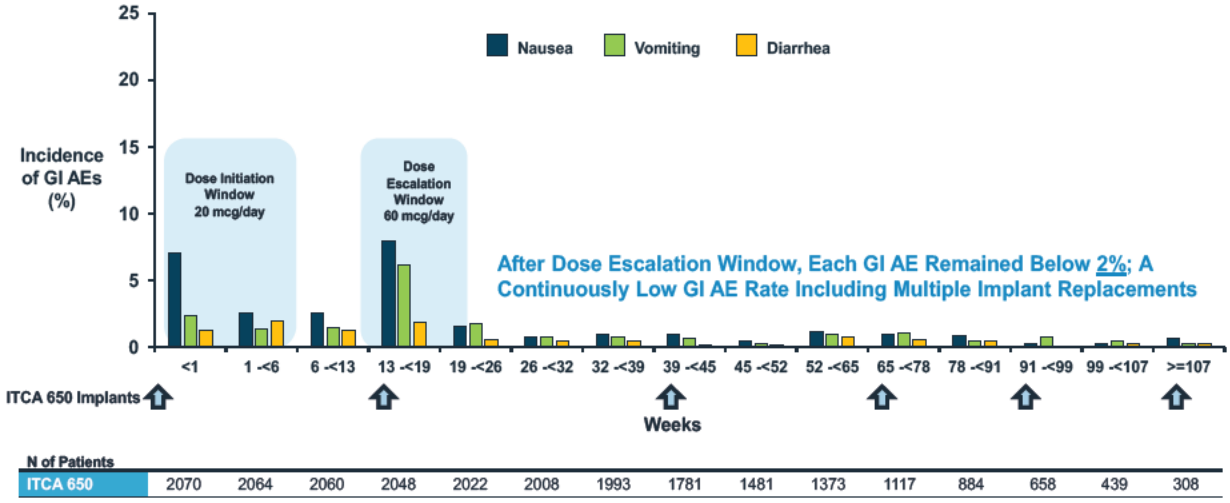
Table 17: Incidence of Gastrointestinal Adverse Events for GLP-1 RAs

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

BID: twice daily; CVOT: cardiovascular outcomes trial; GI AE: gastrointestinal adverse event; QW: once weekly; SAE: serious adverse event
Source: GI AE data in FDA medical reviews/labeling; *CVOT GI AE data where AKI SAE imbalances exist

As with approved GLP-1 RA products, transient periods of higher incidence for GI adverse reactions were observed early during the 6 weeks after dose initiation and in the corresponding 6-week period after dose escalation, illustrated in Figure 22. After these dose initiation and escalation dosing windows, GI AE rates rapidly declined after approximately 19–26 weeks on the 20/60 mcg/day ITCA 650 regimen to low rates of < 2% during continuous maintenance therapy with multiple 6-month maintenance implants.

Figure 22: Study 107 Occurrence of Gastrointestinal Adverse Events Over Time



GI AEs: gastrointestinal adverse events

In patients with pre-existing renal impairment and potential dehydration risk factors, transient GI AEs at dose initiation and dose escalation can contribute to the risk of AKI (Figure 6). Treating clinicians need to understand that dehydration can occur with GLP-1 RAs due to transient nausea, vomiting, and diarrhea, and could be further exacerbated by concomitant metformin (additional GI AEs) and diuretic use.

Concomitant use of metformin, which is used by most patients with T2DM, significantly increases the risk for and severity of nausea and vomiting and needs to be monitored early-on in GLP-1 therapy in patients who have AKI risk factors.

The low and steady rate of GI AEs of < 2% at time points after the two initial dosing periods, along with sustained efficacy throughout the course of study treatment, support the reliable and consistent implant performance and favorable tolerability of ITCA 650 implants across Phase 3 trials, with maintenance therapy durations up to 32 months in Study 107 and significantly longer (up to 4.5 years) in Study 103 HBL.

Overall, use of ITCA 650 as recommended resulted in a GI safety profile as expected for exenatide or other GLP-1 RA therapies. Because ITCA 650 therapy can only be administered in-office settings by trained and certified health care providers, this provision should facilitate appropriate patient education from providers and subsequent oversight, monitoring and educational reminders for patients during the 2 initial dosing windows before rates of GI AEs decline to stable low levels comparable to placebo over time.

7.8.2 Acute Kidney Injury

In the full Phase 3 program (4 RCTs), there were 14 AKI SAEs reported in the ITCA 650 arms and 4 on placebo. Two of the 14 were non-treatment-emergent per Study 107 protocol, and 1 event was in Study 105 in a patient who had a proximal major bleed

associated with the AKI SAE; this event was not considered study drug-related. There were also no AKI SAEs in Phase 3 Studies 103 or 201. Thus, 11 (0.5%) treatment-emergent AKI SAEs in the ITCA 650 arm, compared to 4 (0.2%) on placebo, were observed in CVOT Study 107.

Importantly, and unlike other GLP-1 CVOTs reviewed below, no patients experienced any repeat AKI SAEs, which in renal impaired patients are known to have a 14-fold increased risk of reaching end-stage renal disease (ESRD) and renal replacement therapy (RRT). All ITCA 650-treated patients with treatment-emergent AKI SAEs fully recovered and 6 successfully continued on therapy and finished the CVOT.

To correct the record, there were no serious AKI deaths on drug and no increase in dialysis. Unfortunately, there were 2 of 4 AKI SAEs on placebo associated with deaths.

Additionally, the KDIGO analysis for assessing AKI for Study 107 suggests that the overall number of Grade 2 and above events are small and there is no significant difference between events in patients treated with ITCA 650 or placebo (Table 18).

Table 18: Study 107: KDIGO Grading: Grade 2 and Grade 3 Serum Creatinine Values

Change from Baseline	ITCA 650	Placebo
Total Patients*	2,064	2,067
Grade 2,	6 (0.29)	4 (0.19)
Grade ≥ 3	2 (0.10)	2 (0.10)
Total Grade 2 and above	**8 (0.39)**	**6 (0.29)**

*Number of patients with non-missing serum creatinine, permitting assessment
KDIGO Staging: Grade 0: Serum creatinine < 1.5 times baseline; Grade 1: Serum creatinine 1.5–1.9 times baseline; Grade 2: Serum creatinine 2.0–2.9 times baseline; Grade 3: Serum creatinine ≥ 3.0 times baseline.

A single patient treated with ITCA 650 and one patient treated with placebo underwent short-term dialysis. There were no deaths among patients with AKI SAE cases who were treated with ITCA 650. Two of the 4 AKI SAEs on placebo resulted in deaths.

Complete details on AKI are presented in Sections 0 as part of Clinical Issue 1.

7.8.3 MACE

7.8.3.1 Study 107 (CVOT) + Study 103 and 105 Meta-Analysis Assessment of MACE

To obtain CV event data to be pooled with CV event data from other pivotal Phase 3 studies in a meta-analysis to demonstrate that the upper limit of the 95% CI of the hazard ratio of major adverse cardiovascular events (MACE) in adult patients receiving standard of care for T2DM receiving either ITCA 650 or control, based on the time to first occurrence of any event in the MACE CV composite endpoint (CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina), is less than 1.8.

In an individual-level patient data meta-analysis of 5,151 patients, including two other Phase 3 trials, there were 160 patients with the key secondary outcome of CV death, non-fatal myocardial infarction, or non-fatal stroke, with HR of 1.12 (95% CI: 0.83–1.54) comparing ITCA 650 to placebo. These results meet the FDA guidance pre-specified, pre-approval criterion (upper limit of 95% CI < 1.8) for non-inferiority, p = 0.002 for non-inferiority.

7.8.3.2 MACE + Hospitalization for Unstable Angina from CVOT

The Phase 3 program was designed to evaluate the CV safety profile of ITCA 650 compared to placebo in alignment with FDA guidance for approval of therapies for T2DM. In the event-driven, placebo-controlled Phase 3 trial (Study 107), the safety of the ITCA 650 20/60 mcg/day regimen was evaluated in 4,156 patients with established CV disease and/or risk factors on a variety of approved standard of care background anti-diabetes therapies. In the primary endpoint analysis, these data were pooled with CV event data from the two pivotal Phase 3 studies (Studies 103 and 105) in a meta-analysis of MACE across the Phase 3 controlled trials utilizing the ITT population with censoring at the end of study.

For Study 107 alone, the composite primary outcome of cardiovascular death, non-fatal myocardial infarction, non-fatal stroke or hospitalization for UA occurred in 4.6% (n = 95) of patients in the ITCA 650 group compared to 3.8% (n = 79) of patients in the placebo group (Table 19). These results meet the FDA guidance pre-specified, pre-approval criterion (upper limit of 95% CI < 1.8) for non-inferiority (HR = 1.21, 95% CI: 0.90–1.63, p = 0.004 for non-inferiority).

Table 19: Study 107 (CVOT): MACE Primary Safety Endpoint

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

CI: confidence interval; CV: cardiovascular; CVOT: cardiovascular outcomes trial; HR: hazard ratio; MACE: major adverse cardiovascular events; MI: myocardial infarction

7.8.3.3 CVOT Conclusions

The ITCA 650 CVOT meta-analysis met the pre-specified primary endpoint that was consistent with FDA guidance. Overall, there was a difference of 16 MACE between drug and placebo, non-definitive.

This non-definitive study was intended to be a bridge to a larger and longer-duration post-approval CVOT that is warranted (see Section 9.1 for details).

Additional details on MACE are presented in Sections 8.3 as part of Clinical Issue 2.

7.8.4 Hypoglycemia and Hyperglycemia

The incidence of treatment-emergent AEs of hypoglycemia events was greater with ITCA 650 than with placebo, and hypoglycemia events were more frequently observed in the presence of co-administration of SUs or insulin (Table 20). No patients experienced hypoglycemia in the absence of insulin and SU concomitant medications. Major hypoglycemia was low (0.3% vs 0.2% for ITCA 650 and placebo, respectively).

Fewer patients treated with ITCA 650 experienced hyperglycemia compared with placebo.

Table 20: Incidence of Hypoglycemia and Hyperglycemia (Pooled Safety Population)

Preferred Term	ITCA 650 20/60 mcg/day N = 2,488 n (%)	Pooled Placebo N = 2,228 n (%)
Hypoglycemia*	223 (9.0)	96 (4.3)
Hyperglycemia	61 (2.5)	99 (4.4)

SU: sulfonylurea
*0% of patients experienced hypoglycemia in absence of insulin and SU concomitant medications.

7.9 Safety Conclusions

The safety profile for ITCA 650 is in-line with the well-established safety of exenatide and approved GLP-1s which include class-labeled AKI Warnings. In a head-to-head trial with an approved form of exenatide (Byetta) at the same daily dose (20 mcg/d), ITCA 650 had markedly less GI AEs. The vast majority of GI AEs (> 97%) in Phase 3 were mild to moderate in severity and transient and fully consistent with the GLP-1 RA class.

8 SPONSOR POSITION ON DISPUTED ISSUES

8.1 Introduction

The unequivocal, sustained efficacy of ITCA 650 has not been disputed by CDER. ITCA 650 consistently demonstrated efficacy at a level comparable to all other approved exenatide and GLP-1 RA products. The issues pertaining to the safety and product characterization of ITCA 650 are systematically addressed below.

8.2 Clinical Issue #1: Acute Kidney Injury

8.2.1 Overview of Facts on Record

Intarcia acknowledges that GLP-1 RA products like ITCA 650 carry risk for early-on GI AEs associated with infrequent AKI events as contained in the labeled AKI Warnings for each GLP-1 product. Intarcia also acknowledges that the same pattern of early-on GI AEs was associated with a small numeric imbalance in AKI SAEs in 1 of the 4 Phase 3 trials (Study 107, the CVOT).

However, the facts herein refute CDER's core AKI conclusions for the GLP-1 class, and for ITCA 650. The first assertion that the entire GLP-1 class has no causal association established between GI AEs (a class effect) and pre-renal AKI SAEs is not supported in the thousands of post-marketing AKI events with GI AEs noted (Figures 87,88), or more importantly, in the unfavorable numeric imbalances in early-on GI AEs and serious AKI events in large GLP-1 CVOTs.

Likewise, CDER's assertion that ITCA 650 is the only GLP-1 in the entire class with a causal association established between early-on GI AEs and a small numeric AKI imbalance in a randomized CVOT is also not supported by the totality of facts that GI AEs and associated AKI SAE numeric imbalances exist in liraglutide's and semaglutide's CVOTs.

Facts from the GLP-1 sponsor for liraglutide and semaglutide, using the same standardized MedDRA AKI search terms that Intarcia did, have publicly disclosed unfavorable numeric imbalances in AKI SAEs in liraglutide's LEADER CVOT, and in semaglutide's SUSTAIN-6 CVOT (Figure 28, Figure 29, Figure).

As seen in ITCA 650's CVOT, other GLP-1 CVOTs, and thousands of post-marketing AKI reports on FAERS, transient GI AEs during dose initiation (mostly) and dose escalation are associated with AKI SAEs. This causal association exists most frequently on low GLP-1 initiation doses when GI AEs first happen in the most susceptible patients - and this risk pattern exists for the entire class (Figure 27), as explicitly outlined in GLP-1 AKI Warnings.

The totality of data show the AKI risk is causally associated with transient early-on GI AEs during dose initiation and dose escalation (a well-known GLP-1 class effect). And last, the risk appears to be heightened in patients with pre-existing renal impairment

(mild, moderate, and severe), and concomitant use of one or more medications known to potentially contribute to dehydration and underlying renal dysfunction (diuretics, metformin, ARBs/ACEs, and NSAIDS).

Table 21 provides verbatim wording of the issues raised by CDER and the facts that systematically address each concern. Supporting analyses and data are provided after the table.

Table 21: Summary of Issue 1 (AKI) and Key Facts on Record

Verbatim Issue	Key Facts

"A signal of AKI was evident in the pivotal phase 3 trials of the ITCA 650 clinical development program. A standardized Medical Dictionary for Regulatory Activities query for acute renal failure (ARF) identified reports of AKI serious adverse events in 14 subjects (0.6 percent) who received ITCA 650 versus 4 subjects (0.2 percent) who received placebo."	• **Intarcia acknowledge a numeric imbalance in treatment emergent AKI SAEs in 1 of 4 phase 3 trials in the NDA**
	• **14 AKIs cited by CDER break down into the following:**
	  • **11 (0.5%) treatment-emergent AKI SAEs on drug vs. 4 (0.2%) on placebo in Study 107**
	  • **2 non-treatment-emergent AKI SAE cases in Study 107,**
	  • **1 AKI SAE in Study 105 associated with a proximal major bleed (a well-known cause of AKI not noted in CDER's writeup, and not study drug related).**

"The magnitude of the AKI risk was greater for ITCA 650 than for the marketed exenatide products or for other members of the GLP-1 RA class. Although other drugs in the GLP-1 RA class have a risk of AKI, this information is based on spontaneous post-marketing adverse event reports. The risk of AKI was not detected in the clinical trials that supported the approval of these drugs. In contrast, the risk of AKI was clearly identified in the ITCA 650 clinical trial data. This AKI risk for ITCA 650, compared to other members of the GLP-1 RA class, is particularly concerning because it was identified from these adequate and well-controlled clinical trials, which constitute stronger evidence for assessing a drug's safety than spontaneous post-marketing adverse event reports."	• **Other GLP-1 sponsors have disclosed pre- & post-approval CVOTs that have unfavorable numeric imbalances in AKI SAEs, AKI deaths reported, dialysis, and repeat AKI SAEs** • **All GLP-1s have labeled AKI Warnings due to the thousands of AKI SAEs reported on FDA's FAERS safety database; Moreover, GLP-1 AKI Warnings emphasize the majority of AKIs reported are associated with transient GI AEs typically observed during dose initiation and escalation – this is a known class effect**
"AKI events experienced by participants who received ITCA 650 sometimes resulted in prolonged hospitalization; complications observed in association with AKI events included dialysis and death."	• **No ITCA 650 AKI deaths in NDA; all 11 patients recovered** • **No increase in dialysis; one case on drug, one on placebo** • **2 AKI SAE deaths in Study 107 were patients on placebo**
"Intarcia's proposed risk mitigation measures were inadequate and sufficient risk mitigation approaches could not be identified for the AKI risk identified in the clinical trial data, particularly because serious AKI events occurred in participants who received ITCA 650 who did not have known risk factors (moderate to severe renal impairment or use of concomitant medications that increase the risk of AKI) and serious AKI events were observed with use of both the nominal initial/reduced dose ITCA 650, 20 micrograms (mcg)/day, and the nominal maintenance dose ITCA 650, 60 mcg/day."	• **All 11 AKI SAEs had both labeled AKI risk factors CDER uses in granting class - labeled AKI Warnings and mitigations. AKI can be labeled, monitored and mitigated** • **ITCA 650 has no AKI SAEs in normal renal function; this is not the case for liraglutide and semaglutide in their CVOTs** • **The imbalance in AKIs occurred during low dose initiation and 2 cases at dose escalation, which is when early-on GI AEs and the majority of post-market AKIs are reported on all GLP-1s (AKIs are common on low initiation doses and again at dose escalation as noted in GLP-1 AKI Warnings)**

Verbatim Issue	Key Facts

AKI: acute kidney injury, CVOT: cardiovascular outcomes trial; GI: gastrointestinal; SAE: serious adverse events; CDER: Center for Drug Evaluation and Research; FDA: Food and Drug Administration; FAERS: FDA Adverse Event Reporting System; NDA: New Drug Application

8.2.2 AKI SAEs

8.2.2.1 Overview of Treatment-Emergent AKI SAEs

In Study 107, treatment-emergent AKI SAEs were reported in 11 ITCA 650-treated patients and 4 placebo treated patients (Table 22).

All events were reviewed by an expert panel consisting of physicians with expertise in endocrinology, nephrology, and cardiology, and a former FDA safety reviewer in the diabetes division. Eight of the 11 ITCA 650 events were determined to be possibly or probably related to treatment and each case had multiple concomitant drugs and AKI risk factors involved (see Section 8.2.2.4 and Appendix Section 13.1). Three of the cases were considered unlikely due to plausible alternate etiologies (e.g., one of the cases was due to a major bleed and did not involve any GI AEs). All 11 patients recovered, with 6 remaining on therapy and completing the trial. No serious AKI events in the ITCA 650 arm (or the entire clinical program) led to death.

Of the 4 AKI SAEs on placebo, 2 patients recovered, and 2 AKI SAE were associated with deaths.

Table 22: Summary of Treatment-Emergent AKI SAEs in ITCA 650 Clinical Program

	Study 107 CVOT		Study 105	
	ITCA 650 N = 2,075	Placebo N = 2,081	ITCA 650 N = 263	Sitagliptin N = 257
Treatment-emergent AKI SAEs	11	4	1*,**	0
Pre-existing AKI risk factors*	11*	4	1	-
Recovered	11	2	1	-
Remained on therapy	6	NA	1	-
AKI SAE leading to death	0	2	0	-
Non-treatment-emergent AKI SAEs	2	0	0	0
Underlying renal impairment and/or risk factor	2	-	-	-

AKI: acute kidney injury; ARBs/ACEs: angiotensin receptor blockers/angiotensin-converting enzyme NSAIDS: non-steroidal anti-inflammatory drug; SAE: serious adverse event

* All had baseline mild to moderate renal impairment and concomitant use of multiple medications known to impact hydration status, renal function, and AKI risk (diuretics, metformin, ARBs/ACEs, NSAIDS)

** Not considered drug related, this AKI SAE was associated with a major bleed and other documented risk factors that were not included CDER (pre-existing renal impairment and concomitant medications used)

8.2.2.2 Overview of Non-Treatment-Emergent AKI SAEs

CDER cited two AKI SAE cases that are not treatment-emergent and not caused by ITCA 650. These events are described in Table 23. Between screening and before the first placement of an ITCA 650 implant, the first patient had a progression to stage 3 renal failure – making the situation pre-existing and not treatment-emergent per protocol. The second patient experienced an AKI SAE over 6 weeks after the final removal of ITCA 650 at the end of the trial. This was also not treatment-emergent per protocol and occurred outside the end of treatment portion of the trial. Both cases also had no GI AEs reported. Moreover, it is biologically implausible for an active ingredient with a half-life of less than a day to cause events prior to initiation of therapy or more than 6 weeks after the final removal. After removal, drug exposure is undetectable within 24 hours.

Table 23: CDER-Identified ITCA 650 Non-Treatment-Emergent AKI SAEs

	2 Known AKI Risk Factors						
Sex / Age	Baseline Renal Stage	Concomitant Medications	Days on Therapy at Onset	Transient GI AEs	Baseline SCr Grade (KDIGO)	Medical History	AKI Resolved
M / 63	Moderate (eGFR: 63 mL/min)	Diuretics, ARB, NSAID	Day 1 Prior to treatment initiation	None reported	Grade 1	Already existing moderate renal impairment progressed to Stage 3a renal failure prior to any insertion of ITCA 650 Other factors: Nephropathy, Angina, Ischemic stroke	Yes
M / 65	Mild (eGFR: 80 mL/min)	Diuretics ACE-I	Day 312; 44 days after the trial ended	None reported	None	AKI event occurred 44 days after final removal of ITCA 650 with no GI symptoms Other factors: Hypertension, MI, CABG, Ex-smoker, Sleep apnea	Yes

ACE-I: angiotensin-converting enzyme inhibitor; AE: adverse event; AKI: acute kidney injury; CABG: coronary artery bypass graft; eGFR: estimated glomerular filtration rate; GI: gastrointestinal; KDIGO: Kidney Disease Improving Global Outcomes; MI: myocardial infarction; NSAID: non-steroidal anti-inflammatory drug; SCr: serum creatinine

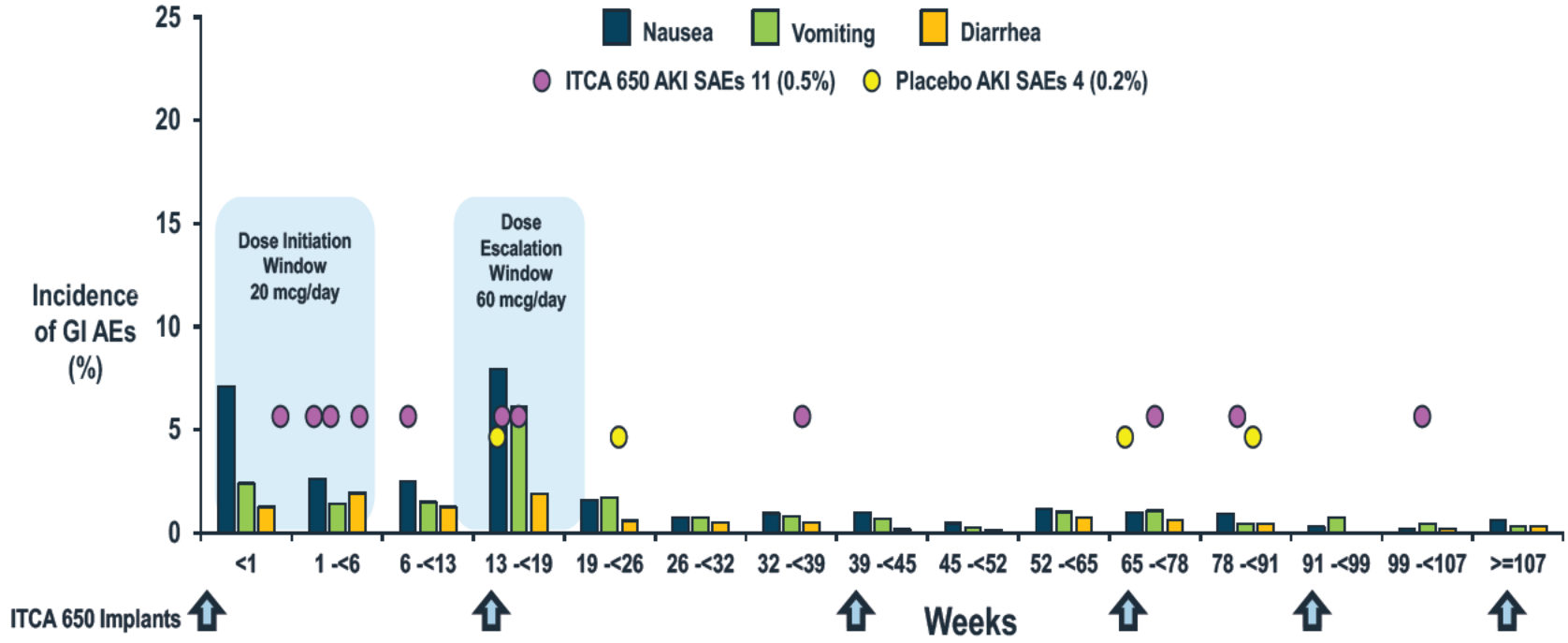
8.2.2.3 Timing of Treatment-Emergent AKI SAEs

A temporal relationship between onset of nausea, vomiting and/or diarrhea and the AKI SAEs was observed in most of the cases in Study 107, the CVOT. This is expected and fully consistent with the AKI onset timing and pattern of AKIs reported on all GLP-1s

given that early-on GLP-1 GI AEs are a known class effect during dose initiation and dose escalation. Thousands of GLP-1 post-marketing AKI reports show that early-on GI AEs (mostly on the lower initiation doses over the first 2-3 months) are the key GLP-1 risk factor that contributes to pre-renal AKI events, as further described in Section 8.2.3.

Figure 23 shows the numeric imbalance in AKI SAEs for ITCA 650 as purple dots and placebo as yellow, demonstrating that the numeric imbalance occurred early during dose initiation, and dose escalation – when transient nausea, vomiting, and diarrhea occurred in a subset of patients. Then AKI events vs. placebo balanced out after the dose escalation window when GI AEs declined to low levels of < 2% at additional time points during maintenance therapy where multiple implants were removed/replaced without any meaningful impact on GI AEs.

Figure 23: Study 107 Incidence of GI AEs & Numeric AKI Imbalance During Dose Initiation & Escalation



AKI: acute kidney injury; GI AE: gastrointestinal adverse event; SAE: serious adverse event

After dose escalation when GI tolerance developed and GI AEs dropped to less than 2% at time points during maintenance therapy, the AKI risk balanced out vs. placebo and aligned with the background rate on placebo in this population (Table 24). This timing of events is predictable and is fully aligned with the GI AE and AKI pattern reported and emphasized with existing GLP-1 class labeled AKI Warnings which currently state the following:

> ***"Acute Kidney Injury:*** There have been ***postmarketing reports of acute renal failure*** and worsening of chronic renal failure, which may sometimes require hemodialysis. Some of these events were reported in patients without known underlying renal disease. ***A majority of the reported events occurred in patients who had experienced nausea, vomiting, diarrhea, or dehydration.*** Some of the reported events occurred in patients receiving one or more medications known to affect renal function or hydration status. Altered renal function has been reversed in many of the reported cases with supportive treatment and discontinuation of potentially causative agents, including VICTOZA®. *Use caution when* ***initiating*** ***or escalating doses*** *of* [GLP-1] ***in patients with renal impairment".***

Table 24: Study 107 Timing of AKI SAE During the Treatment Period

	ITCA 650 20/60 mcg/day N = 2,070	Placebo N = 2,074
AKI SAEs during low dose initiation and dose escalation window	7 (0.33%)	1 (0.04%)
AKI SAEs after dose escalation window during maintenance therapy	4 (0.19%)**	3 (0.14%)

ACE: angiotensin-converting enzyme; AKI: acute kidney injury; ARB: angiotensin receptor blockers; GI AE: gastrointestinal adverse event; NSAIDs: non-steroidal anti-inflammatory drugs; SAE: serious adverse event;
* AKI Risk Factors Involved In Each Case: All patients had pre-existing renal impairment; All patients on one or more con-meds known to increase GI AEs, dehydration, and renal dysfunction; metformin, diuretics, ARBs/ACEs, and NSAIDs
** Note: 1 of the 4 cases noted after dosing was due to a serious bleed/transfusion and no GI AEs that was not study drug related

8.2.2.4 Summary of Individual AKI SAEs

Table 25 summarizes the AKI SAEs reported in patients who received ITCA-650. In most cases, these patients experienced transient GI events of nausea, vomiting, or diarrhea (majority reported as mild/moderate). Importantly, all AKI SAEs resolved.

All ITCA 650- treated patients who experienced AKI in Study 107 had underlying risk factors for AKI:

- 11 of 11 had underlying renal impairment (mild (eGFR < 90 ml/min to moderate eGFR < 60 ml/min) at baseline; No AKI SAEs were observed in ITCA 650 patients with healthy renal function in the ITCA 650 NDA (~30% of patients on

drug in NDA). However, the same is not true in GLP-1 AKI post-marketing events and/or the reported AKI SAE imbalances noted in the CVOTs for liraglutide and semaglutide where numerous AKI SAE cases on liraglutide and semaglutide actually occurred in patients with normal/healthy renal function at baseline.

- 11 of 11 patients were on one and many times more than one concomitant medication known to impact hydration status, renal function, and AKI risk (i.e., diuretics, metformin, ARBs/ACEs, NSAIDs).

All patients treated with placebo who experienced AKI SAEs in Study 107 also had underlying risk factors. Two of 4 patients on placebo with AKI SAEs died.

Table 25: ITCA 650 Summary of AKI SAEs by Study and Patient

Sex / Age	2 Known AKI Risk Factors		Days on Therapy at Onset of AKI	GI AEs	Creatinine at event (KDIGO Grade)	Patient Recovered
	Baseline Renal Impairment	Concomitant Medications				
M / 76	Mild (eGFR: 63 mL/min)	Metformin, diuretic, ARB	Day 7	Mild/Mod Nausea, Diarrhea	Grade 3	Yes
M / 62	Mild (eGFR: 87 mL/min)	Metformin, 3 diuretics, ACE-I	Day 8	Mild Nausea, Vomiting	Grade 3	Yes
M / 73	Mild (eGFR: 62 mL/min)	Metformin	Day 8	Mod Nausea, Vomiting, Diarrhea	Grade 2	Yes
M / 67	Mild (eGFR: 68 mL/min)	Metformin, NSAID, ACE-I	Day 19	Mod Vomiting	Grade 3	Yes
F / 68	Moderate (eGFR: 57 mL/min)	Metformin, diuretics, ACE-I	Day 75	Mod Nausea, Vomiting, Diarrhea	Grade 1	Yes
M / 43	Moderate (eGFR: 48 mL/min)	Metformin, ARB	Day 111	Mild/Mod Vomiting	Grade 1	Yes
M / 74	Mild (eGFR: 62 mL/min)	Metformin, diuretics, ACE-I	Day 117	Severe Diarrhea	Grade 2	Yes
F / 75	Mild (eGFR: 64 mL/min)	Metformin, NSAIDs, ARB, Antibiotics	Day 281	Mild Vomiting	Grade 3	Yes
F / 66	Moderate (eGFR: 58 mL/min)	Metformin, ARB	Day 500	No GI AEs; Major Bleed	Grade 2	Yes
F / 64	Mild (eGFR: 83 mL/min)	Metformin	Day 559	Mod Vomiting, Diarrhea	Grade 3	Yes
M / 73	Moderate (eGFR: 50 mL/min)	Metformin, NSAID,	Day 748	Mod/Severe Nausea,	NA	Yes

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

Medical History

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

AKI: acute kidney injury; Scr: serum creatinine

Table 26: Summary of Placebo Patients with AKI SAEs

Sex / Age	2 Known AKI Risk Factors		Days on Therapy at Onset	GI AEs	Creatinine at Event (KDIGO Grade)	Patient Recovered
	Baseline Renal Impairment	Concomitant Medications				
Study 107 (CVOT)						
F / 70	Mild (eGFR: 65 mL/min)	Metformin, Amoxycillin – clavulanate, ARB, diuretics	Day 107	NR	Grade 3	Yes
M / 71	Moderate (eGFR: 55 mL/min)	Metformin, ARB, acetylsalicylic acid	Day 168	None	Grade 3	AKI SAE Resolved **But Died 32 Days Later**
M / 67	Mild (eGFR: 87 mL/min)	Metformin, Antibiotic use	Day 460	Vomiting	Grade 2	No; **Patient Died**
F / 62	Mild (eGFR: 80 mL/min)	Metformin, ACE-I, acetylsalicylic acid	Day 632	Diarrhea	Grade 2	Yes

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

8.2.3 Known GLP-1 RAs Class Risk for AKI SAEs

8.2.3.1 Existing AKI Warnings and Precautions with GLP-1 RA Products

Hypovolemia (low blood volume) is one of the most common causes for AKI, usually caused by dehydration or excessive bleeding.

Because of this, and the GLP-1 post-marketing AKI reports in the FDA FAERS database, all GLP-1 products carry a Warning for AKI risks associated with transient GI AEs at dose initiation (mostly) and dose escalation that can contribute to pre-renal AKI events. The GLP-1 class-labeled AKI Warnings derived from all of the post-marketing AKIs reported clearly state:

> **"a majority** of the reported **[AKI SAEs]** occurred in patients who had **experienced nausea, vomiting, or diarrhea,** leading to volume depletion."

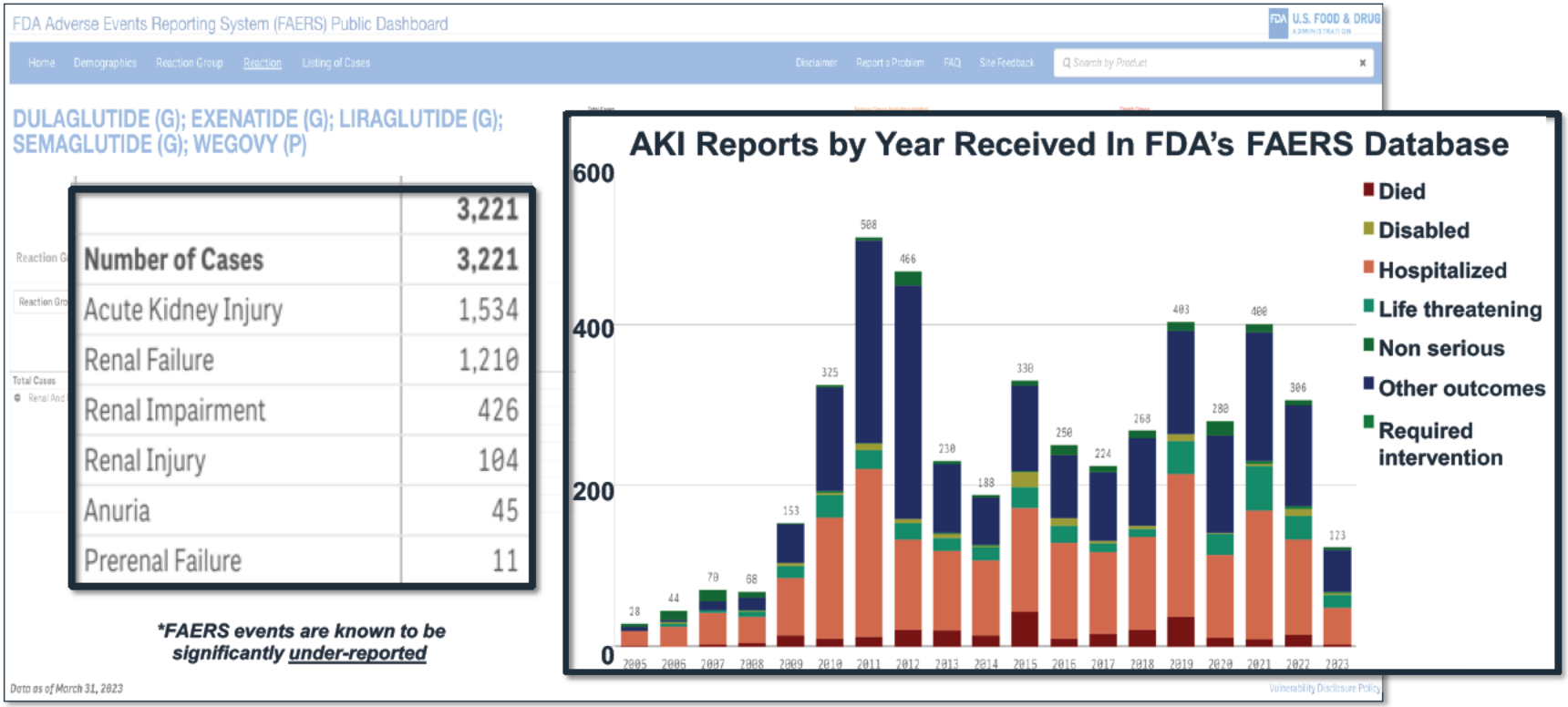
In addition, the AKI Warnings state:

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

The acknowledgement of early-on GI AEs as a class effect and a causally associated risk factor is important and very prudent given the AKI SAE numeric imbalances in CVOTs and in numerous post-marketing events. Furthermore, the facts related to these potentially life-threatening events in both treatment settings show the same patterns and a highly plausible biological mechanism and class effect (i.e., GI AEs at dose initiation and escalation that can lead to infrequent pre-renal AKIs) for all GLP-1 products. The same type of class labeling would be expected for ITCA 650 along with exenatide specific renal impairment labeling to align with exenatide products on the market.

Figure 24 shows the FAERS pharmacovigilance data reporting AKI events for five GLP-1 products. These AKI data from FDA's signal detection network, which are also known to be significantly under-reported, support the ongoing need for proactively communicating this risk, monitoring it closely (particularly early-on) and mitigating this early-on GI AE and AKI risk in proper labeled Warnings and risk mitigations for every GLP-1 product.

Figure 24: GLP-1 AKI Post-Marketing Reports in FDA's FAERS Safety Database – By Year Reported



** Since clinical trials often lack the power to detect rare SAE signals, spontaneously reported events are useful in detecting safety signals. However, no cross-product comparisons, relative risk & definitive causality can be made. The actual numbers of cases reported is known/published to likely represent only a small % (as low as 10%) of the actual cases that occur in a real-world setting.

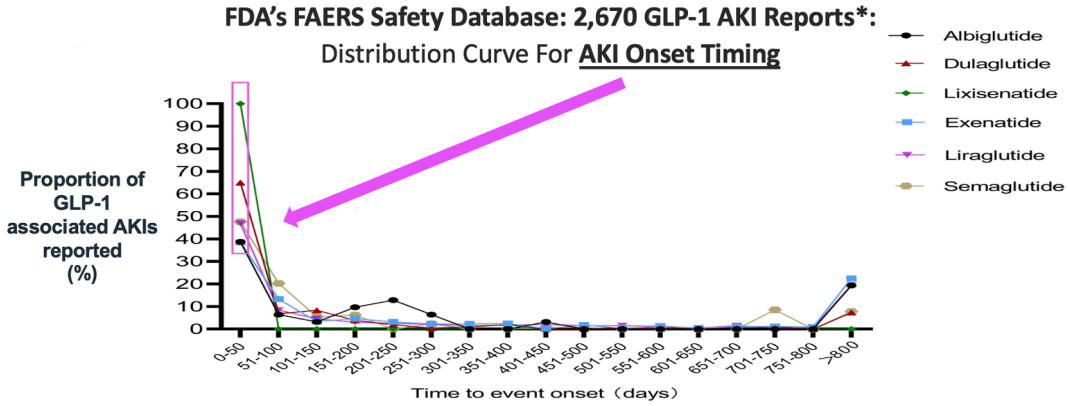
Importantly, due to the data in Figure 23 and reporting details for these AKI cases, FDA notes in all current GLP-1 AKI Warnings that **"a majority** of the reported [**post-marketing AKIs**] occurred in patients who had **experienced nausea, vomiting, or diarrhea,** leading to volume depletion**"**.

The emphasis in FDA's GLP-1 AKI Warnings on **the majority of AKIs being associated with GI AEs** at **dose initiation** and **dose escalation** is fully consistent with the literature for the GLP-1 class and is strongly supported by a recent FDA FAERS publication assessing AKI patterns with all approved GLP-1s. (FAERS database, Dong 2022)

The FAERS publication on GLP-1s and AKI events outlines a timing of AKI onset analysis done for each of the GLP-1 AKI cases in the FAERS safety database as of 2022 (2,670 AKI reports associated with GLP-1s). The AKI onset timing analysis shows that the majority of GLP-1 serious AKI post-marketing events occur quite early-on during lower dose GLP-1 initiations where it is known that GI AEs are common in a subset of the most susceptible patients (Figure 25). The authors of the publication who plotted the onset of the 2,670 AKIs reported on GLP-1s noted that some of the reported AKIs started within days on all GLP-1s, and that most of the cases reported happened on the lower initiation doses during the first 1-3 months. Additional AKI events are also reported after the first few months (particularly during additional dose escalations) for the class as transient GLP-1 GI AEs are also known to occur with dose escalations as well.

In summary, the AKI onset timing data show a clear and consistent AKI pattern for the GLP-1 class where the majority of AKI cases reported are happening in susceptible patients during the initiation a GLP-1 on the lower doses where GI AEs are common in a subset of patients. Additional AKIs can and do occur during dose escalation/s as well when GI AEs are transiently elevated for a period of time before declining to low levels on most GLP-1s during maintenance therapy as GI tolerance develops. These insights are invaluable for AKI labeled Warnings and risk mitigation for the entire GLP-1 class.

Figure 25: FDA's FAERS Safety Data On GLP-1 Post Marketing AKI Reports*: Early AKI Onset Timing Shows Majority of AKIs Are On the Low Initiation Doses



FDA's AKI Warnings For All GLP-1s[1] Emphasize The Association & Timing Of GI AEs:

"**A majority** of reported **[AKIs]** occurred in patients who experienced **nausea, vomiting, or diarrhea,** leading to volume depletion"[1]

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

FAERS: FDA Adverse Events Reporting System
* FAERS 2,670 AKI Events Reported On GLP-1s During 2004-2021.
Source: FAERS database, Dong 2022

1. FDA's labeled AKI Warnings referring to these post-marketing events for approved GLP-1s

8.2.3.2 Numeric Imbalances in Serious AKIs with GLP-1 Products In CVOTs

CDER's AKI Concern:

> **"The Numeric Imbalance in AKI SAEs in Study 107 (CVOT) Suggests ITCA 650 Causes AKI to a Greater Extent Than Other GLP-1s Which Did Not Show Numeric Imbalances in Large, Randomized Trials (CVOTs)"**
>
> **(Page 44 of CDER's Proposed Order to Deny ITCA 650).**

To address this concern, Intarcia conducted an assessment using randomized CVOTs and standardized AKI SAE MedDRA narrow scope search terms for each of the CVOTs with public AKI SAE data available. Intarcia captured all reported serious AKI events in each arm of the study for drug and placebo, including reported repeat AKI SAEs, as repeat AKI SAEs in patients with existing renal impairment are known to be associated with a 14-fold increased risk of reaching ESRD and RRT (Sykes 2019).

Randomized data with numeric imbalances in AKI SAEs, sometimes including reports of AKI SAE associated deaths and increased dialysis, have been reported in several GLP-1 RCTs for approved products. Specifically, GLP-1 sponsors and investigators

have publicly disclosed data from the SUSTAIN-6 CVOT and the LEADER CVOT showing that unfavorable numeric imbalances in AKI SAE exist for semaglutide and liraglutide (Figure 26).

Figure 26: Standardized MedDRA AKI SAEs Reported GLP-1 CVOTs

Sponsor Disclosed Facts: Numeric Imbalances In AKI SAE Events [1,2,3]

ITCA 650 CVOT Study 107 N = 4,156	ITCA 650 N = 2,075	Total AKI SAE Events	Placebo N = 2,081	Total AKI SAE Events
Total AKI SAEs	11 (0.5%)	11	4 (0.2%)	4

Semaglutide SUSTAIN-6 CVOT N = 3,297	Sema 0.5 mg N = 826	Total AKI SAE Events	Placebo 0.5 mg N = 824	Total AKI SAE Events
Total AKI SAEs	26 (3.1%)	30	18 (2.2%)	18

Liraglutide LEADER CVOT N = 9,340	Lira N = 4,668	Total AKI SAE Events	Placebo N = 4,672	Total AKI SAE Events
Total AKI SAEs	141 (3%)	164	136 (2.9%)	153

Note: Not head-to-head CVOTs. Comparison of small imbalances in serious adverse events does not imply anything about comparable safety or magnitudes of risk. Data plainly show ITCA 650 is not the only GLP-1 with a small numeric imbalance in AKI SAEs in a CVOT.

[1] CDER's Proposal To Deny ITCA 650 @ p.44 asserted only ITCA had a small numeric AKI imbalance in a CVOT
[2] Source Of Standardized MedDRA AKI SAE Reporting: Sustain-6 AKI SAEs @ ClinicalTrials.gov; ITCA 650 Study 107 CSR In NDA; LEADER AKI SAEs In Sponsors EMDAC Table 19, page 75 of 95
[3] Total AKI SAEs required reporting (including repeat AKI SAEs) are critical to include in AKI risk assessments. Subjects with renal impairment and repeat AKI SAEs have a 14-fold increased risk of reaching ESRD/RRT

None of these small numeric imbalances were statistically significant but they exist, and not surprisingly, the unfavorable numeric imbalances were associated with GI AEs that were proximal to the serious AKI events and hospitalizations. On semaglutide, and liraglutide in particular, there were also upwards of 23 repeat AKI SAEs and hospitalizations that hold a 14-fold increased risk of reaching ESRD and renal replacement therapy.

In addition to the unfavorable numeric imbalances in serious AKIs in Figure 26 for all three GLP-1s, non-serious + serious AKIs (i.e., total AKI events) were also unfavorably imbalanced across all three CVOTs for ITCA 650, semaglutide, and liraglutide Figure 27.

In fact, in CDER's correspondence with Intarcia during FDRR in 2020, (footnote on Figure 26) noted that unfavorable numeric imbalances observed with both serious and non-serious AKIs only adds weight to the fact that the unfavorable imbalances in serious AKI are real. And that the totality AKI data further supports that AKIs are a causally associated risk with GLP-1 treatments. One clearly associated with early-on GI

AEs and important to acknowledge as a causally associated risk for the GLP-1 class (which is not the case right now in CDER's proposed order) so that it can be better managed through Warnings, renal monitoring, and significantly more education about how to proactively mitigate it with providers and their patients.

Figure 27: Numeric Imbalances in Both Serious + Non-Serious AKIs in CVOTs: Adds Weight[1] to Totality of Data That Numeric Imbalances In AKI SAEs Are Real

Unfavorable Numeric Imbalances In Both Serious & Non-Serious AKIs

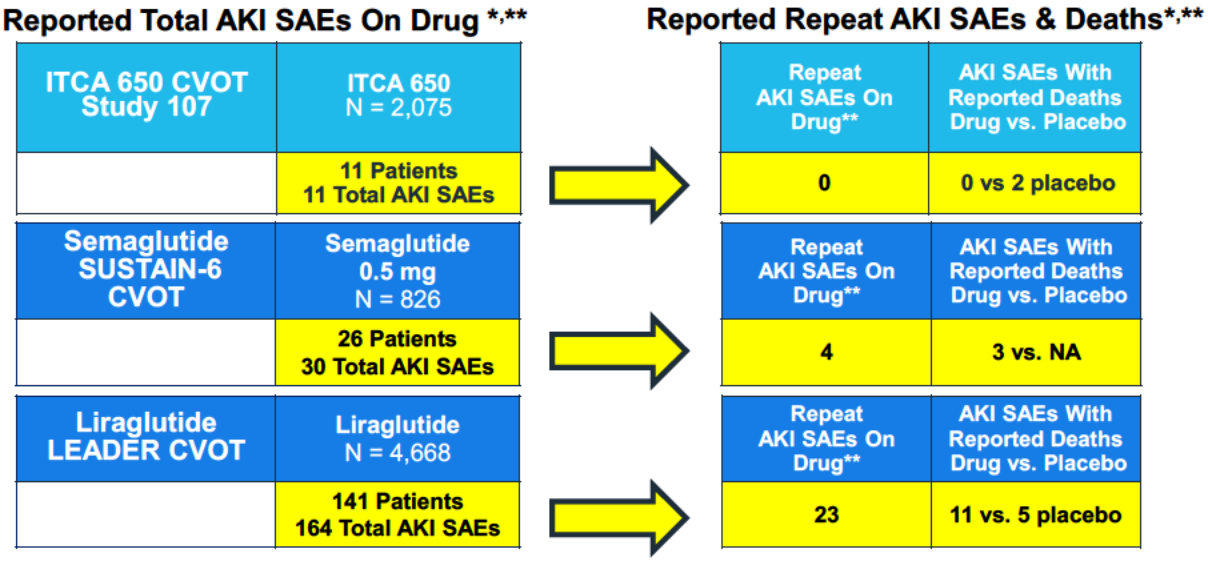
GLP-1 CVOTs	(Serious AKI + Non-Serious) Drug vs Placebo	Serious AKI Alone Drug vs Placebo
ITCA 650 CVOT[2] N=2075	1.9% vs 1.2%	0.5% vs 0.2%
SUSTAIN-6 CVOT[3] N=826	5.1% vs 4.1%	3.1% vs 2.2%
LEADER CVOT[4] * N=4668	4.8%* vs 4.5%	3.0%* vs 2.9%

* Note: The AKIs reported above omit important "repeat" AKI SAEs (23 on liraglutide) where CKD patients with 'repeat' AKI SAEs have a 14-fold increased risk of ESRD / RRT.
[1] CDER FDRR letter 7/30/2020 p.8 "The numbers of serious [AKI] adverse events are relatively small; however, similar imbalances are also observed in the analyses of all adverse AKI events [non-serious + serious AKIs]. With the [AKI] analyses expanded to all adverse events, and greater numbers of events, the results support the [numeric imbalance] findings observed for the serious adverse events."
[2] ITCA 650 NDA; AKI Expert Report In NDA and CSR Study 107
[3] Semaglutide SUSTAIN-6 Randomized AKIs on 0.5 mg drug vs. 0.5 mg volume-matched placebo control published in NEJM, 2016; Semaglutide SUSTAIN-6 serious AKI imbalance reported on ClinicalTrials.gov
[4] Liraglutide EMDAC Materials: Sponsor Reported Serious and Non-Serious AKI Events In LEADER EMDAC Materials (p.75)

Additionally, the serious AKIs reported on both liraglutide and semaglutide 0.5 mg in the same two CVOTs had AKI SAE deaths reported, as well as multiple reports of repeat AKI SAEs with the increased risk in reaching ESRD and RRT (Figure 28). While the risks of repeat AKI SAEs and hospitalizations are serious in terms of accelerating ESRD and RRT, Intarcia does not have access to the patient level data for each AKI SAE death reported on liraglutide and semaglutide in their CVOTs. We've provided our knowledge of the facts regarding deaths reported because it was asserted in error that ITCA 650 was associated with AKI deaths.

Importantly, there were no AKI SAE deaths nor any repeat cases of AKI SAEs in the entire ITCA 650 program.

Figure 28: Complications Associated with AKI SAEs Reported in GLP-1 CVOTs



Note: Not head-to-head CVOTs. Comparison of small imbalances in serious adverse events does not imply anything about comparable safety or magnitudes of risk. Available data do not support CDER's assertion that ITCA 650 was associated with more AKI SAE deaths.

* Source Of Standardized MedDRA AKI SAE Reporting: Sustain-6 AKI SAEs @ ClinicalTrials.gov; ITCA 650 Study 107 CSR In NDA; LEADER AKI SAEs reported In Sponsors EMDAC Table 19, page 75
** **Total AKI SAEs Includes Repeat AKIs & Hospitalizations; Renal Impaired Patients (Majority in CVOTs) with Repeat AKI SAEs Have 14-Fold Increased Risk Of Reaching ESRD/Renal Replacement Therapy (RRT)**
*** Relative risk (95% CI) on ITCA 650 Is 2.76 (0.88, 8.65); FDA relative risk (95% CI) on semaglutide is 1.44 (0.80, 2.61); Lira info to calculate NA. Relative risk calcs do not factor in Repeat AKI risks for ESRD/RRT.

The totality of serious AKI data on liraglutide and semaglutide, including the AKI deaths reported, the cases of dialysis reported, and the multiple repeat cases of AKI SAEs reported do not support that ITCA 650 confers a unique or greater AKI risk than that which is known in other large and well conducted GLP-1 CVOTs.

ITCA 650 is not the only GLP-1 with a small numeric imbalance in a CVOT trial. As the evidence shows, it is also not accurate to contend that approved GLP-1s don't have small numeric AKI imbalances and/or any serious AKI causal associations identified with proximal GI AEs from their large, well randomized CVOTs. The pattern of transient GI AEs at dose initiation and escalation that leads to infrequent pre-renal AKI events is seen in both randomized CVOTs as well as post-marketing events for the GLP-1 class.

Acknowledging these class effects and the same biologically plausible mechanism for the class in both treatment settings will help to raise awareness of the risk and how to proactively label, monitor and mitigate it, particularly in those most at risk.

As just one example, Intarcia can share that to our knowledge the AKI SAE imbalance in SUSTAIN-6, where a total of 30 AKI SAEs that were reported in 26 patients for

semaglutide 0.5 mg compared with 18 AKI SAEs on 0.5 mg volume-matched placebo control (Figure 25) were not made public in any prior regulatory proceeding, other than in materials related to this hearing.

These randomized data were not reported in the Sponsor's 2017 EMDAC materials or in CDER's EMDAC or NDA review documents. Despite serious AKI being a medical event of special interest and a pre-specified SAE requiring expedited reporting, the primary randomized AKI safety data in each of the two SUSTAIN-6 dosing arms was not disclosed the way it was pre-specified in the sponsor's protocol and SAP. The sponsor pooled parts of the 0.5 mg AKI SAE safety data in their EMDAC materials and only reported a smaller portion of the 0.5 mg AKI SAEs per standard MedDRA AKI search terms that were **greater than > 1%.** That means that all the AKI SAE MedDRA search terms and events < 1% were excluded from what the sponsor disclosed to the EMDAC.

Had all the standard MedDRA AKI narrow scope search terms been presented as posted for SUSTAIN-6 on Clinicaltrials.gov, as first added by the same sponsor after the EMDAC, they would have showed the EMDAC that there were actually 30 total serious AKIs on the 0.5 mg dose vs 18 on 0.5 mg of volume-matched placebo, including 3 AKI SAE reported deaths on the 0.5 mg arm.

But the sponsor only presented a subset of the 0.5 mg AKI SAE MedDRA search terms that were > 1% (see Sponsor's EMDAC Briefing Document, Table 21; p. 100 of 158) making it erroneously appear that there was a numeric imbalance in AKI SAEs in favor of semaglutide 0.5 mg vs. placebo. This is opposite the actual randomized and fully disclosed serious AKI facts on record in the opposite direction not favoring the 0.5 mg dose (Table 27).

Table 27: SUSTAIN-6 Total AKI SAEs in 0.5 mg vs 1.0 mg Treatment Groups

Semaglutide SUSTAIN-6 CVOT* AKI SAEs	Semaglutide 0.5 mg				Semaglutide 1.0 mg			
	Sema 0.5 mg N = 826	Total AKI SAEs	Placebo 0.5 mg N = 824	Total AKI SAEs	Sema 1.0 mg N = 822	Total AKI SAEs	Placebo 1.0 mg N = 825	Total AKI SAEs
Total AKI SAEs Reported	**26 (3.1%)**	**30**	**18 (2.2%)**	**18**	**10 (1.2%)**	**12**	**24 (2.9%)**	**26**
Acute Kidney Injury	18 (2.2%)	22	14 (1.7%)	14	6 (0.7%)	8	22 (2.7%)	24
Renal Impairment	3 (0.4%)	3	3 (0.4%)	3	1 (0.1%)	1	1 (0.1%)	1
Renal Failure	2 (0.2%)	2	1 (0.1%)	1	3 (0.4%)	3	1 (0.1%)	1
Acute Prerenal Failure	1 (0.1%)	1	0 (0%)	0	0 (0%)	0	0 (0%)	0
Azotemia	1 (0.1%)	1	0 (0%)	0	0 (0%)	0	0 (0%)	0
Anuria	1 (0.1%)	1	0 (0%)	0	0 (0%)	0	0 (0%)	0

Source: SUSTAIN-6 Study Results on ClinicalTrials.gov; Standard MedDRA v 18 Narrow Scope Search Terms
Total AKIs (serious + non-serious) are also imbalanced on 0.5 mg: 42 (5.1%) vs 34 (4.1%) placebo; NEJM 2016
N = Number of patients randomized; Total AKI SAEs Captured as Repeat AKI SAEs have 14-fold Increased Risk of ESRD and RRT
AKI Are Treatment Emergent / "In Trial" = From Time of First Dose to End Follow Up

In prior communications, CDER has obscured the 0.5 mg AKI SAE imbalance by using unblinded post hoc pooling of all the AKI SAEs across the two different randomized dosing arms (i.e., 0.5 mg and 1.0 mg arms, each with volume-matched placebo controls shown above) even though the SUSTAIN-6 protocol explicitly pre-specified them as comparisons to each other over the two-year treatment, and not to be pooled.

While pooling data across similar trials using the same doses is done as an exploratory analysis at times, safety pooling is not done in a single multi-dose trial where two or more different doses are purposefully being compared to determine if there are any dose and/or time dependent differences in safety that would obviously never be detected if you only viewed post hoc pooled data.

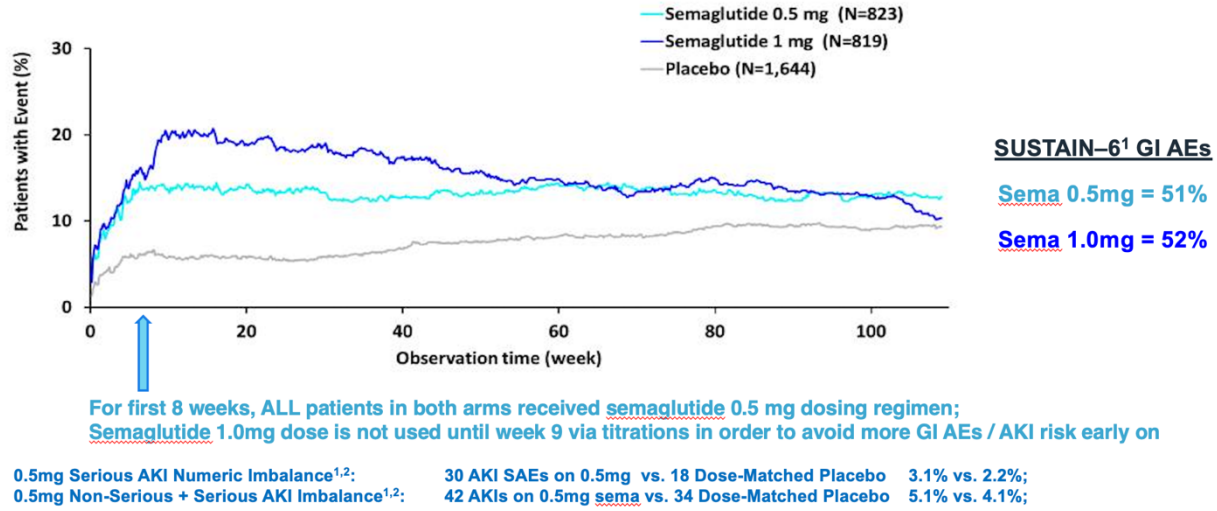
Thus, the unblinded and post-hoc pooling of two different doses also does not follow the FDA 2018 Pooling/Meta-Analysis Guidance document which outlines several very sound scientific principles regarding when it is appropriate or not appropriate to pool important safety data for regulatory decision making (FDA 2018 Meta-Analysis Guidance). Pooling Sustain-6 AKI SAEs after the AKI SAE data and deaths were already unblinded violates each of the core scientific principles outlined.

Consideration about unblinded pooling should also be given to the fact that serious AKI was already a class-labeled Warning prior to these semaglutide findings and not disclosing the randomized serious AKI data on 0.5 mg vs. the 0.5 mg dose-matched

placebo control obscured the unfavorable serious AKI imbalance and 3 reported deaths observed on the 0.5 mg dosing arm.

Avoiding pooling that could mask a serious AKI imbalance between doses is critically important - especially when all patients begin on the lower 0.5 mg dosing arm for the first two months prior to titration to the higher 1.0 mg dose. The majority of the post-marketing AKI SAEs reported on semaglutide occurred very early-on during the first two months on the 0.5 mg initiation dose (Figure 25) with the majority of cases involving GI AEs at dose initiation and escalation as noted in the labeled AKI Warnings. The same 0.5 mg dose has the unfavorable serious AKI imbalance that exists in SUSTAIN-6 and should not be pooled post hoc (Figure 26, 27, 28).

Figure 29: SUSTAIN-6 GI AEs Over Time & 0.5 mg AKI Imbalances Reported



GI AEs: gastrointestinal adverse events
[1] SUSTAIN-6 Clinicaltrials.gov; SUSTAIN-6 publication NEJM, 2016
[2] EMA SUSTAIN-6 EPAR p.115: In the CVOT, "all AKI AEs and SAEs were associated with chronic renal disease",,, and some were temporally associated with GI AEs"

It is important to remember that the 1 mg semaglutide dose has nothing to do with early-on GI AEs and AKIs in the first 2 months of therapy where AKIs are most commonly observed. This is because the 1.0 mg dose is purposefully not used at all during the first 2 months of therapy to mitigate and avoid higher rates of GI AEs and AKI risk.

This differential timing and AKI pattern by dose (including 1.0 mg not being used at all the first 2 months) demonstrates the need for separate examination of the randomized AKI SAEs by dose over time, which was the sponsors pre-specified intention in SUSTAIN-6. There is no basis to do an unblinded "post hoc pooling" of the 0.5 mg data on an already labeled AKI Warning with life-threatening consequences.

Table 28: Semaglutide 0.5 mg AKI Signal & Post Hoc AKI Pooling

Primary Randomized Data[1]: AKI SAE Imbalance incl. 3 Deaths	Semaglutide 0.5 mg N = 826	Dose-Matched Placebo 0.5 mg N = 824
SUSTAIN-6 Total AKI SAEs	30 AKI SAEs	18 AKI SAEs

	Unblinded Post Hoc Pool Both Sema Dosing Arms[2] 0.5 mg + 1.0 mg N = 1,648	Unblinded Post Hoc Poo Both Sema Placebo Arms 0.5 mg + 1.0 mg N = 1,649
Post Hoc Pooling of Total AKI SAEs[1,2]	42 AKI SAEs	44 AKI SAEs

1. AKI SAEs (MedDRA Narrow Scope) Found on Clinicaltrials.gov Total AKIs (serious + non-serious) imbalanced on 0.5 mg: 42 (5.1%) vs 34 (4.1%) placebo; NEJM 2016

2. 1 mg dose had 12 total AKI SAEs vs dose-matched 1 mg placebo which had 26 total AKI SAEs. The reduction in 1.0 mg AKIs was seen in year 2 and have nothing to do with 0.5 mg AKIs (during dose initiation/escalation).

8.2.4 AKI Events Leading to Death

As noted, to address statements about AKI deaths in CDER's proposed order, there were no deaths due to AKI SAEs in patients receiving ITCA 650 nor any increase in dialysis vs. placebo. There was only one case of short-term dialysis in each treatment group. The 11 patients with treatment-emergent AKI SAEs on ITCA 650 all recovered, and 6 successfully completed the trial.

Once CDER recently agreed that none of the AKI SAEs in Study 107 led to any fatalities, their Proposed Order raised 2 non-serious AKIs where CDER stated they believed there may have been "reasonably association" with deaths. The facts below show the two AKIs were not drug related and also that the 2 patients died from other causes not related to study drug as described in Table 29.

Table 29: Study 107 (CVOT) 2 Deaths Associated with Non-Serious AKI with Alternative Causation Shown in Case Report Forms

Sex / Age	2 Known AKI Risk Factors: Baseline Renal Stage	2 Known AKI Risk Factors: Concomitant Medications	Days on Therapy at Onset of AKI	GI AEs	Creatinine at event (KDIGO Grade)	Medical History	AKI Resolved
M / 68	Mild (eGFR: 88 mL/min)	Diuretics, ACE, NSAID	649	Yes (Day 642) due to viral gastro-enteritis that resolved	NR	T2D, hypertension, coronary artery disease, severe sleep apnea, UA, dyslipidemia, prostate cancer, kidney stones. Non-serious viral gastroenteritis causing dehydration/GI AEs, with secondary non-serious case of AKI that quickly resolved. Not drug related.	Resolved (Day 652)
			747	No (Day 747) no proximal GI AEs. GI bleed is proximal to AKI		100 days later readmission for NSTEMI and found secondary AKI. Transferred to another hospital same day and found to have hematemesis and a significant ongoing GI bleed (hemoglobin 7.2g/dl) that was related to the acute renal failure requiring dialysis (eGFR 13, creatinine 4.38 mg/dl). Patient had worsening multi-organ dysfunction syndrome and died.	No; Died on Day 755 due to multi-organ dysfunction syndrome (Not study drug related)
M / 66	Moderate (eGFR: 54 mL/min)	Metformin, ACE-I / HCTZ	110	No proximal GI AEs	NR	History of T2D, hypertension and CKD. Non-serious AKI related to worsening renal disease. eGFR 43 and creatine of 1.61, 4 months earlier eGFR was 54 and creatine of 1.33 Patient was instructed to stop metformin. Patient was with family in morning watching TV and found dead later in day from a coronary event not related to drug.	No; Died of Acute Coronary Event (Not study drug related)

AE: adverse event; AKI: acute kidney injury; CKD: chronic kidney disease; CV: cardiovascular; eGFR: estimate glomerular filtration rate; GI: gastrointestinal; NR: not reported; UA: unstable angina

The sequence of events leading to death for the 68-year-old male are described below. This case was determined to be not study drug related due to the proximal major GI bleed that likely led to the AKI and the fact that there was no involvement of GI AEs.

- Day 642: Diagnosis by the investigator noting non-serious viral gastroenteritis was the cause of dehydration/GI AEs.
- Day 649: Seven days later went to ER for chest pain. Admitted for chest pain and developed a secondary non-serious case of AKI that resolved on Day 652.
- Day 747 (100 days later): Patient presented for 2–3 days of chest pain and was admitted with diagnosis of (NSTEMI). A secondary AKI was diagnosed (no proximal GI AEs). The patient was treated with heparin and intravenous (IV) fluids and quickly transferred to another hospital for additional tests on same day.
- Day 747: Upon admission patient had hematemesis and was quickly diagnosed with a significant ongoing GI bleed (hemoglobin 7.2 g/dl) and related acute renal failure requiring dialysis (eGFR 13, creatinine 4.38 mg/dl). Hypotension, worsening respiratory failure/ARDS, and multi-organ dysfunction syndrome worsened. Patient died on day 755.
- Cause of Death: Multiple organ dysfunction syndrome (not study drug related).

The sequence of events leading to death for the 66-year-old male were as follows:

- Day 110: Non-serious AKI related to worsening CKD. Creatine was 1.61 vs 1.33 4 months earlier. No reported GI AEs. The patient was instructed to stop metformin.
- Day 119: Family was with patient in morning and found patient deceased at home later the same day.
- Cause of Death: Acute coronary event (Investigator and coroner noted due to natural causes; assessed as not study drug related).

8.2.5 *AKI Labeling & Risk Management*

The facts strongly support that early-on GI AEs and AKI risk are not isolated to only ITCA 650. GI AEs at dose initiation and dose escalation are a well-established class effect and should be emphasized as a known and causally associated risk factor for infrequent pre-renal AKI events for all GLP-1 drugs in the class.

The numeric AKI imbalance seen with ITCA 650 in the CVOT population conforms to the two early and well-defined dose initiation and dose escalation periods where GI AEs are transiently elevated before they decline to < 2% for maintenance therapy thereafter. This aids in making labeled Warnings, monitoring and risk mitigation effective.

In addition to monitoring renal function in renal impaired patients with transient GI AEs and educating patients about the risk of AKI if dehydration occurs, we also know that all 11 patients treated with ITCA-650 had both of the same AKI risk factors that are in the labels for approved GLP-1s already. This includes awareness of concomitant medications that impact hydration status (e.g., diuretics), and others that impact renal function and AKI risk.

Mitigation of AKI risk is also enabled by the required in-office dosing and administration coupled with proactive patient education on important Warnings and precautions given to providers and patients proactively upfront.

In summary:

AKI can be mitigated with labeling, monitoring, and proactive measures (Bettge 2017)

- Advise potential GI AEs at dose initiation/escalation, and risk of AKI if dehydration occurs
- Advise to avoid dehydration if GI AEs occur; any evidence of dehydration, treat accordingly
- Monitor renal function when clinically indicated and especially in renal impaired patients who may experience early-on transient GI AEs
- If dehydration/renal impairment is evident, modify or stop suspected meds (inc. ITCA 650)

A GLP-1 AKI Warning for ITCA 650 is justified by facts, precedence, and benefit / risk

- Note: The ability to stop GLP-1 therapy is critical with any AKI SAE; When ITCA 650 is removed it eliminates drug levels in < 24 hours vs 5-8 weeks on long-acting injectable GLP-1s

8.2.6 AKI Conclusions

GLP-1 GI AEs at dose initiation & dose escalation are a class effect and an established risk factor for pre-renal AKIs for the GLP-1 class as a whole. The active ingredient in ITCA 650 is exenatide – with a well-established GLP-1 safety profile.

Transient early-on GI AEs on both low initiation doses and escalation doses have led to AKI SAEs in post-marketing reports and small AKI SAE numeric imbalances in multiple GLP-1 randomized, controlled CVOTs.

The ITCA 650 data support the same established AKI risk factors and the infrequent risk of AKI that other products in the class have seen in RCTs and thousands of post-marketing AKI events reported and on record with FDA. This warrants an approval with an applicable GLP-1 class AKI Warning.

Furthermore, from a benefit/risk perspective, ITCA 650 offers a new maintenance therapy option where ensured patient adherence can be given by a provider every 6 months. This helps address a widespread unmet need in the US by eliminating the need to rely on daily or weekly self-administration when known glucose control and poor adherence challenges exist. Thus, doctors and patients can maintain exenatide efficacy just twice yearly that has been repeatedly demonstrated in all 4 RCTs in the ITCA 650 NDA.

Please see Appendix Section 13.1 for detailed investigations and conclusions by an independent renal expert for all AKI SAEs in Study 107.

8.3 Issue #2: MACE

8.3.1 Overview of Facts on Record

The CVOT study fulfilled pre-approval requirements in accordance with the well-established FDA Guidance for Industry (FDA 2008 CV Risk Guidance). The facts provide sufficient assurance, pre-approval, that ITCA 650 is not associated with excess CV risk and which is consistent with 2008 CVOT guidance available at time the study was conducted and precedent for T2DM products. This was reaffirmed by the EMDAC at the 24–25 October 2018 meeting.

Table 30 provides the facts that systematically addresses each cited concern for this issue. Supporting analyses and data are provided after the table.

Table 30: Summary of Issue 2 (MACE) and Key Facts on Record

Verbatim Issue	Key Facts
"A prespecified meta-analysis incorporated the data from clinical trials CLP-103, CLP-105, and CLP-107, and included 181 MACE and unstable angina (UA) events. An unfavorable point estimate of 1.12 was observed [hazard ratio (HR) for MACE + UA; 1.12 (95 percent confidence interval (CI): 0.83, 1.51)]."	• **CVOT met FDA's primary endpoint requirements on meta-analysis and CVOT** • **HR (95% CI) = 1.12 (0.83 – 1.51) non-inferiority: p=0.002**
"The cardiovascular risk assessment failed to provide sufficient assurance that ITCA 650 is not associated with excess cardiovascular (CV) risk. Rather, the clinical trial data suggested that ITCA 650 may be associated with an increased risk for major adverse cardiovascular events (MACE), defined as myocardial infarction, nonfatal stroke, and cardiovascular death."	• **Met FDA requirement for CI upper bound < 1.8 needed to bridge to post-approval CVOT** • **HR (95% CI) = 1.21 (0.90 – 1.63) non-inferiority: p=0.004**
"Furthermore, estimates of CV risk from the meta-analysis were notably higher and nominally statistically significant in the subgroup of participants 65 years of age or older [HR for MACE + UA; 1.67 (95 percent CI: 1.02, 2.71)]. Subgroup analyses also suggested an interaction between CV risk and baseline renal function, where the HR estimates trended higher with worse renal function."	• **1 of 34 subgroups, only 69 MACE events** • **Analyses of small subgroups with high Type 1 error risk** • **Subject to misleading conclusions**
"This CV risk resulting from ITCA 650 use is particularly concerning when compared to the beneficial effect of other drugs in this class on CV outcomes. In contrast to the unfavorable CVOT results for ITCA 650, some other GLP-1 RA products carry indications for MACE risk reduction in patients with T2DM based on favorable results of CVOTs. The MACE HR observed in a CVOT conducted for another formulation of exenatide was 0.91 (95 percent CI: 0.83, 1.0). The lower bound of the CLP-107 confidence interval (0.90) nearly excludes the point estimate for MACE risk observed with this other product (0.91), suggesting a true difference in MACE risk between the products."	• **Studies showing benefit are much larger, longer, and with significantly more events and power** • **For example, the LEADER CVOT had 9,340 patients, nearly 3× the duration, and 7.5× the MACE events in Study 107** • **CV benefit is not a requirement pre-approval; proper post-approval CVOT needed to assess CV outcomes**

CI: confidence interval; CV: cardiovascular; CVOT: cardiovascular outcomes trial; FDA: Food and Drug Administration; HR: hazard ratio; MACE: major adverse cardiovascular events

8.3.2 Study 107 CVOT Successfully Fulfilled Regulatory Requirements for a Novel Antidiabetic Product

Study 107 was designed in accordance with the 2008 FDA pre-approval guidance, FDA Guidance for Industry: Diabetes Mellitus - Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes (December 2008), in place at the time the ITCA 650 CVOT was conducted and then submitted in the NDA. The guidance outlines requirements for CV evaluation of adjudicated MACE to ensure that a new therapy is not associated with an unacceptable increase in cardiovascular risk:

- The upper bound of the two-sided 95% CI for the estimated risk ratio should be less than 1.8.
- If the pre-marketing application contains clinical data that show that the upper bound of the two-sided 95% CI for the estimated increased risk (i.e., risk ratio) is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a post-marketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95% CIs for the estimated risk ratio is less than 1.3.

Note: The recommended number of exposures has changed since the CVOT was conducted. A draft guidance became available in March 2020, replacing the prior 2008 guidance (Draft Guidance for Industry: Type 2 Diabetes Mellitus: Evaluating the Safety of New Drugs for Improving Glycemic Control). This draft version explicitly states that the guidance "should be viewed only as recommendations," while the prior recommendations were pre-approval requirements for submission. Notably, the new guidance makes no mention of CVOT studies to assess MACE or thresholds for approval since "none of the CVOTs to date have identified an increased risk of ischemic CV events."

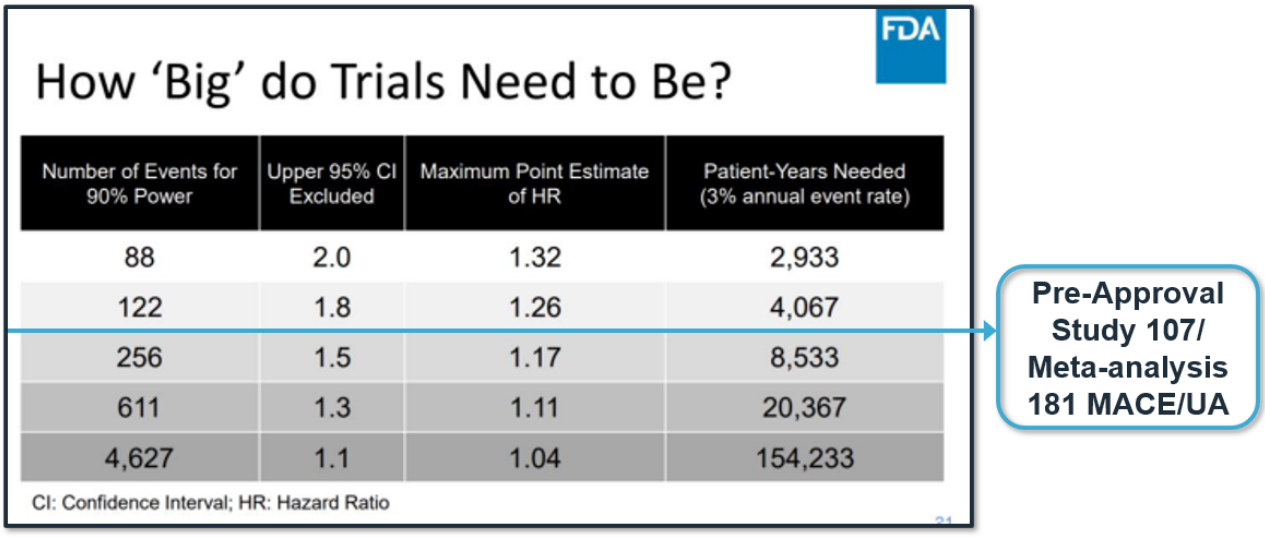
Study 107 and the pre-specified CVOT meta-analyses met the pre-specified requirement to exclude 1.8 as the upper bound of the 95% CI for the time to first MACE occurrence, demonstrating that ITCA 650 will not result in an unacceptable increase in cardiovascular risk. The HR for the meta-analysis endpoint was 1.12 (95% CI: 0.83, 1.51), p=0.002. The planned post-approval CVOT is described in Section 9.

As a short-term pre-approval CVOT that was powered to support submission but not definitively determine MACE risk, there were relatively few CV events (MACE) in Study 107. For three-point MACE (MACE-3; cardiovascular death, nonfatal MI, or nonfatal stroke), there were 85 and 69 events in the ITCA 650 and placebo groups, respectively. For four-point MACE (MACE-4; cardiovascular death, nonfatal MI, nonfatal stroke, or hospitalization for unstable angina), there were only 95 and 79 events, respectively. For either endpoint, therefore, the difference between treatment groups was only 16 patients.

8.3.3 Meta-analysis for MACE Results Based on Small Number of Events, as Designed

The meta-analysis of Studies 107 (CVOT), 103, and 105 was designed in accordance with FDA pre-approval guidance. When compared to powering estimates presented by the FDA at the 24–25 October 2018 EMDAC, the number of MACE reported for the meta-analysis (181 aligns with the estimated maximum point estimate and upper bound as shown in Figure 30).

Figure 30: MACE Outcomes Align with FDA's Powering Estimates



CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiovascular events; UA: unstable angina
Pre-Approval Study 107 had 174 MACE+UA
Source: FDA Presentation Slides, EMDAC Meeting 24–25 October 2018

8.3.4 Exploratory Subgroup Analyses

MACE was evaluated in 34 exploratory analyses, which included only 69 events creating a high Type 1 error risk. For these analyses, it is important to keep in mind that there was no correction for multiplicity in these 34 analyses. Thus, although the HR of MACE + UA for patients ≥ 65 years old was 1.67 (95% CI: 1.02, 2.71), placing too much weight on result can lead to misleading conclusions.

Notably, a multivariate analysis did not find that age > 65 to be an independent predictor of outcome. Age will also be evaluated in the post-approval CVOT which will enroll a sufficient number of patients at least 65 years old to further assess this important patient cohort.

8.3.5 Comparison of MACE Results to Other GLP-1s

Claims of MACE risk reduction with other GLP-1s are drawn from larger, longer studies, with more events and power, usually designed as post-approval studies. LEADER, for example, had 9340 patients, and 7.5 times the MACE reported for Study 107. Study 107

was neither powered nor of sufficient duration to allow for any other assessment. Thus, it is not appropriate to compare to larger and longer definitive post-marketing trials studies of other members of the class.

As illustrated in Table 31, precision can change with a longer or larger study. The Lixisenatide pre-approval MACE results from 263 total events were consistent with FDA guidance, at the time, and align with ITCA 650's pre-approval CVOT data. Only during the post-approval extension with longer duration that captured more than 800 events did the upper bound of the 95% CI fall below 1.3, with the point estimate lowering as well. Non-inferiority was met but not superiority.

Table 31: Example Comparison of Pre- and Post-Approval MACE Results (Lixisenatide)

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

CI: confidence interval; HR: hazard ratio; MACE: major adverse cardiovascular events; UA: unstable angina
Source: CDER Lixisenatide Review

8.3.6 Conclusions

Study 107, designed as a pre-approval CVOT with a meta-analysis of Study 103 and 105 included, achieved its objective, **HR (95% CI) = 1.12 (0.83 – 1.51); non-inferiority p = 0.002.** This result met CDER's pre-approval criteria with an upper bound of the 95% CI < 1.8. This study was designed, once the criteria were met, to bridge into a larger and longer-duration post-approval CVOT which is warranted. An adequately powered study with sufficient duration to achieve more definitive MACE is planned to be conducted post-approval to assess CV safety, and potential for benefit with twice-yearly maintenance dosing (see Section 9.1).

8.4 Issue #3: Drug Delivery and Product Performance

8.4.1 Overview of Factual Errors

There are important factual corrections for the record regarding drug delivery and product performance, each of which are outlined and addressed below. The established DUROS® technology that the exenatide release mechanism is based on met pre-defined IVR upper and lower limit specifications demonstrating stable and consistent release with limits over the 3- or 6-month implant dosing intervals. The lower

limit was set based on efficacy, and the upper limit was set based on safety, and clinically validated in Phase 2 and extensive Phase 3 trials in nearly 6,000 patients.

More than 22,000 devices were used in Phase 3 trials and performed as designed. The clinical data from thousands of ITCA 650 implants have validated that the implants have substantial evidence of efficacy and safety for the intended use. Both the 3- and 6-month maintenance implants produced unequivocal glucose lowering efficacy that was sustained and consistent in all 4 ITCA 650 RCTs and reinforced by a safety profile that is squarely in-line with exenatide and the other approved GLP-1 products on the market with AKI labeled Warnings that were justified by the same GI AE pattern and numeric AKI imbalance risk observed in Study 107 (CVOT).

Table 32 provides the facts that systematically addresses each concern for this issue.

Supporting analyses and data are provided after the table.

Table 32: Summary of Issue 3 (Dose Delivery) and Key Facts on Record

Verbatim Issue	Key Facts
The device design validation data did not support the proposed daily, weekly, and biweekly in vitro drug-release specifications as appropriate for the intended use.	• **The upper and lower IVR specification limits were acceptable at the end of Phase 2 meeting with FDA, used successfully in all 4 successful RCTs in the NDA, and further tightened and met based on input from FDA during first cycle NDA review** • **The additional device design validation data did support the in vitro drug-release upper and lower limit specifications**
The in vitro device performance data demonstrated inconsistent day-to-day drug delivery and did not support that weekly and biweekly in vitro drug release testing is adequate to ensure controlled in vivo drug release by the device constituent of ITCA 650.	• **Phase 3 and registration lots on the 3- and 6-month implants met the pre-specified weekly and bi-weekly IVR upper and lower limits for the full intended use periods of the devices** • **Both weekly and daily IVR testing shows that ITCA 650 implants performed within pre-specified weekly and daily IVR specification limits for the intended use**
Clinical data to validate the upper and lower limits of device IVR specifications not shown safe/effective for intended use	• **Extensive clinical data from 4 successful RCTs validate the upper and lower IVR limits as unequivocally effective, and with overall safety including GI AEs that are squarely in-line with GLP-1s & existing GLP-1 class-labeled AKI Warnings** • **The totality of AKI evidence shown for the GLP-1 class and ITCA 650 strongly supports that ITCA 650 is not the only GLP-1 with a small numeric imbalance in AKI SAEs associated with GI AEs at dose initiation and dose titration. The same pattern happens in post-marketing events and imbalances exist in other CVOTs.**

AKI: acute kidney injury; CVOT: cardiovascular outcomes trial; GI AE: gastrointestinal adverse event; IVR: in vitro release; New Drug Application; RCT: randomized controlled trial; SAE: serious adverse event

8.4.2 IVR Controls and Testing Results

8.4.2.1 IVR Upper and Lower Limits Met & Tightened by Sponsor

Specifications

The ITCA 650 uses an established DUROS® osmotic implant technology used with the previously approved product, VIADUR (leuprolide acetate). The same initial weekly and bi-weekly IVR intervals used with ITCA 650 were also used with VIADUR: 0–14 days (Interval 1); 14–28 days (Interval 2); and 28–42 days (Interval 3). As explained in the approval documents for VIADUR, “The time intervals were selected to characterize the implant system in its initial drug release startup phase, and then at steady state.” Further, as shown below in this section, FDA has accepted a “tri-phasic” drug release startup phase followed by a variable release with Bydureon’s injectable depot delivery system, an injectable exenatide product on the market.

ITCA 650 uses an osmotic pump that relies on physiological interactions to operate. After implantation, the product experiences a rapid change from room temperature to body temperature. The temperature change results in a small formulation volume expansion, and a small quantity of formulation releases. There is an inherent lag in the startup of drug delivery from the mini-pumps, coinciding with the time required to reach a steady-state flux of water through the semi-permeable membrane of the osmotic engine. The membrane must imbibe an initial quantity of water to establish an osmotic pressure gradient between the environmental fluid and the interior of the osmotic engine. Once the osmotic pressure gradient has been established, water diffuses through the semi-permeable membrane at a relatively constant rate based on the presence of a saturated salt solution within the osmotic engine.

Once the implant delivery system reaches steady-state, there is a constant delivery of the exenatide formulation at a predetermined delivery rate using the fundamental physics of osmosis. The speed of the piston is determined by the rate of water absorption through the membrane, which was tested by Intarcia and tightly controlled by specifications to deliver the suspension formulation at a constant rate for the intended duration of use (91 days/3 months or 182 days/6 months).

The IVR rate is a key quality attribute that predicts in vivo drug delivery. The critical factors (which are controlled) that affect IVR include: the rate of water uptake by the mini-pump through the semi-permeable membrane, implant manufacturing specifications, and the exenatide concentration in the suspension. The IVR rate is evaluated by measuring the mass of exenatide released in specified time intervals from the implants.

The method used for routine quality control (QC) measurement of the IVR rate of exenatide from ITCA 650 devices was developed and validated for weekly and biweekly measurements and has been used to characterize and verify the design and performance of ITCA 650 devices and for routine QC testing for the devices used in all

4 successful clinical studies in the NDA. Previously approved products using the same DUROS® osmotic implant technology used the same IVR approach and measures as well. The ITCA 650 IVR assay measures the weekly or biweekly exenatide released from ITCA 650 implants for the full intended use durations.

ITCA 650 reliability is ensured through IVR specifications, which have been rigorously evaluated, enhanced over time, and even further tightened post successful Phase 3 data in all 4 RCTs. During the first cycle of NDA review, Intarcia addressed a request from CDER to tighten the upper and lower limit IVR specifications (Table 33).

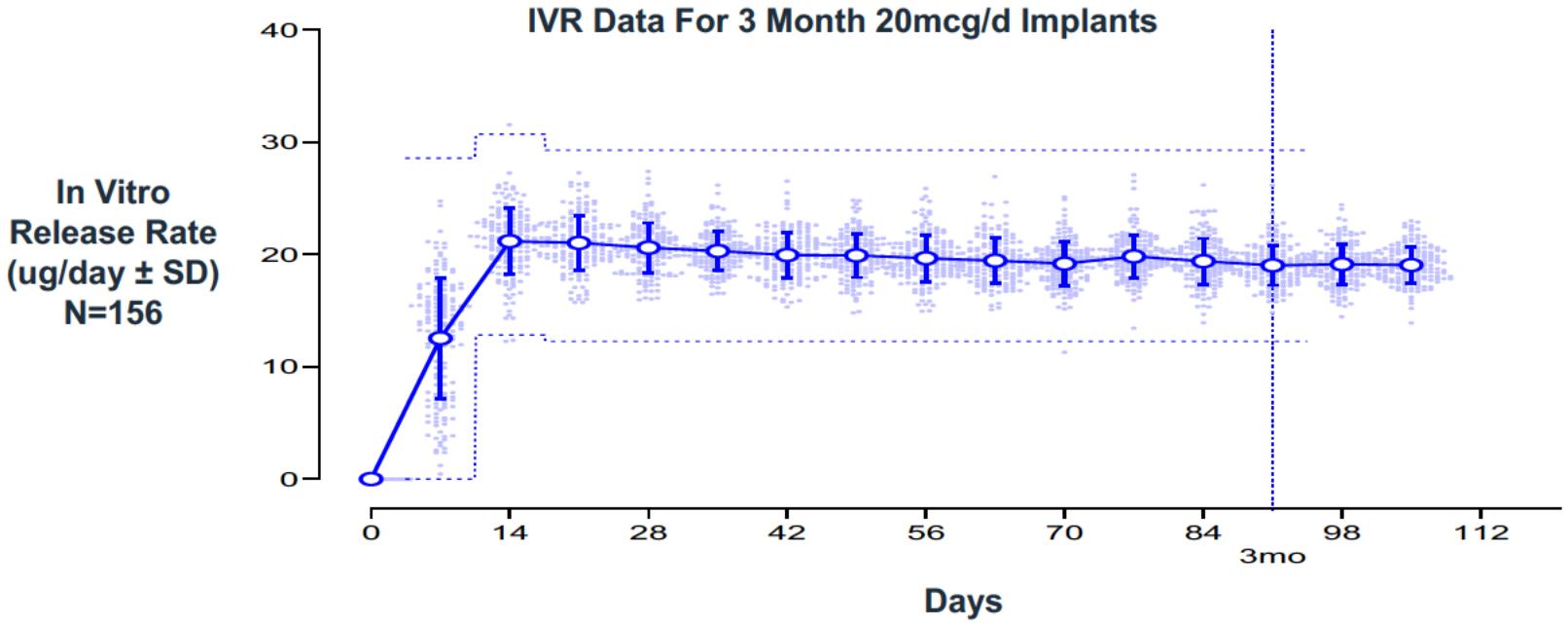
Table 33: History of IVR Specifications for 60 mcg/Day 6-Month Dosage Strength – Proposed Specifications Consistent with Intervals Recommended by FDA

		Interval	1 (0–14 days)	2 (14–28 days)	3 (28–42 days)	4 (70–84 days)	5 (126–140 days)	6 (168–182 days)
IVR Specifications Requested by the Agency (Dated 26Jul2017)	Level 1 Stated Range (mcg)	Lower limit	501	767	738	NA		
		Upper limit	**1093**	**1091**	**1088**			
		Midpoint	797	929	913			
		Allowed Range	±37%	±17%	±19%			
Proposed IVR Specifications In Prior NDA Resubmission	Level 1 Stated Range (mcg)	Purpose	Lot Release and Stability			Stability		
		Lower limit	420	715	640	640	640	640
		Upper limit	**980**	**1075**	**1025**	**1025**	**1025**	**1025**
		Midpoint	700	895	833	833	833	833
		Allowed Range	±40%	±20%	±23%	±23%	±23%	±23%

The IVR ranges for Intervals 1 and 2 take into consideration the startup of the pumps, while the ranges for the other intervals represent steady-state delivery. The upper limits for Intervals 1, 2, and 3 are lower than FDA requested limits. Also, per CDER's request, Intarcia added steady state intervals 4, 5, and 6 and used the specifications for testing of 12 units (vs 6) per lot consistent with USP <724>. ITCA 650 Phase 3 clinical and registration lots perform within these upper and lower limit IVR specifications.

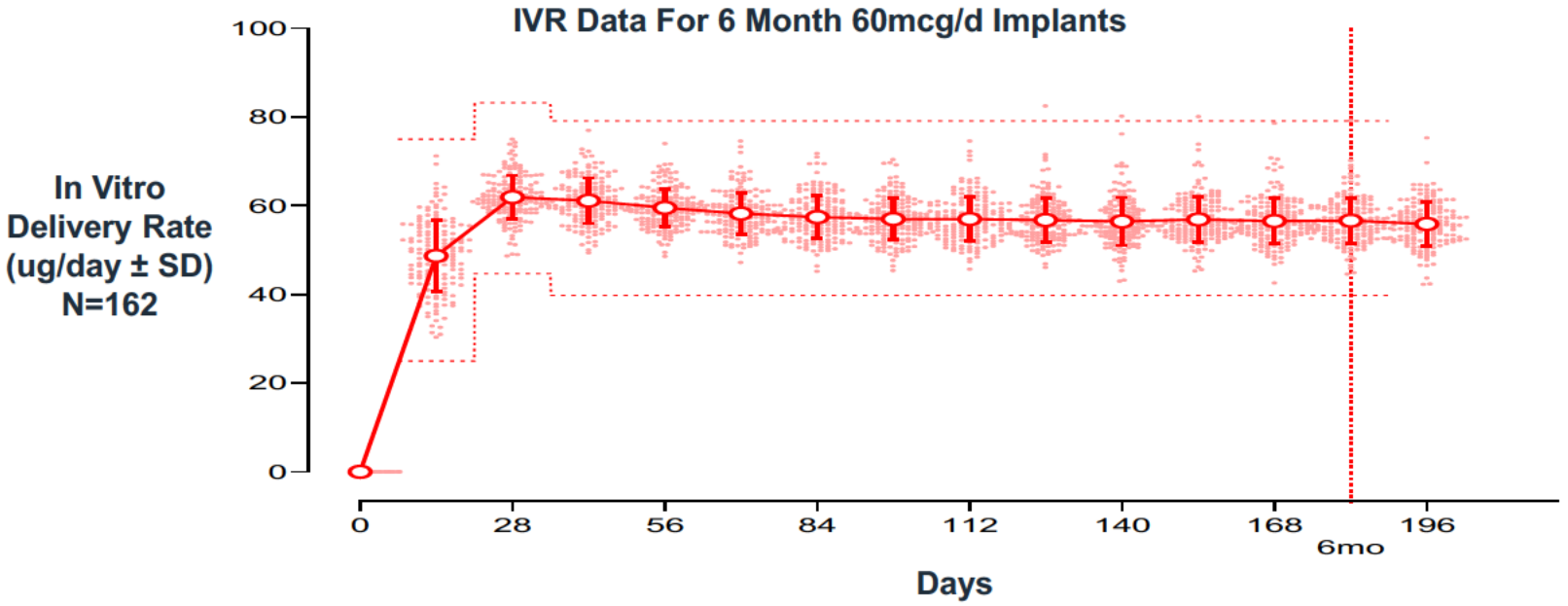
The IVR data for ITCA 650 implants measures and demonstrates the continuous and consistent release of exenatide within pre-specified upper and lower IVR limit specifications for the full in-use period of 3- or 6-months for each implant, as show in Figure 31 and Figure 32 below, respectively.

Figure 31: ITCA 650 3 Month Implants: IVR Data from 3 Phase 3 / Registration Lots Shows Consistent Exenatide Delivery Within Set Upper and Lower IVR Limits



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

Figure 32: ITCA 650 6 Month Implants: IVR Data from 3 Phase 3 / Registration Lots Shows Consistent Exenatide Delivery Within Set Upper and Lower IVR Limits



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

Delivering exenatide within the pre-specified IVR upper and lower limit specifications (per USP 724) ensures continuous exenatide delivery that has been clinically validated as highly effective and safe for the intended/labeled use. As shown herein, substantial and highly consistent evidence of efficacy was established in each clinical trial in the NDA and the safety and tolerability profile in all 4 RCTs was in line with overall AEs and incidence of GI AEs that are a known class effect and a labeled risk factor in AKI Warnings for all approved GLP-1 products.

Upper and lower IVR limits were evaluated weekly and biweekly throughout the program and the clinical and registration show consistent cumulative release within the pre-specified IVR upper and lower limits.

Daily IVR Data

After the first CRL focused on the AKI issues addressed, CDER and CDRH asked Intarcia to develop new IVR methods to perform a one-time daily IVR study on clinical lots of 3- and 6-month implants, with the objective of seeing if there was dose dumping or any pattern of major daily outliers within the traditional weekly or bi-weekly IVR limits used throughout Phase 2 and Phase 3. Intarcia invested significant time to develop new methods and performed the daily IVR testing experiments during the full 3- and 6-month use durations and included resulting data in the second NDA submission in 2019. Daily IVR testing shows that all daily IVR acceptance criteria were met and ITCA 650 performed as designed for the full intended use durations of 3 and 6 months. For all sampling intervals, acceptance criteria were met with 95% confidence and 80% reliability for the initial week, and 95% confidence and 90% reliability were met for the rest of the in-use period.

The measured daily IVR test results, when extrapolated to weekly and biweekly rates, complied with the proposed QC specification. Further, the average delivery rates were comparable between daily and weekly/biweekly measurements.

The Phase 3 and registration lots devices performed within the pre-specified upper and lower limit acceptance specifications noted below and in order to correct the misinterpretation noted below (Figure 33 and Figure 34).

Figure 33: ITCA 650 20 mcg/day Implants - Upper and Lower Limits of IVR Specifications

FDA Misinterpreted IVR Specification

FDA Interval	Daily Range (mcg)	% of 20 mcg Target Range
0-14 Days	2 – 40	10 – 200%
14-91 Days	10 - 36	50 – 180%

Intarcia IVR Specification

Intarcia Interval	Daily Range (mcg)	% of 20 mcg Target Range
0-7 Days	1 – 27	3 – 136%
7-14 Days	15 – 29	75 – 143%
14-21 Days	14 – 27	71 – 136%
35-42 Days	14 – 27	
63-70 Days	14 – 27	
84-91 Days	14 – 27	

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

FDA Misinterpreted IVR Specification

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

Intarcia IVR Specification

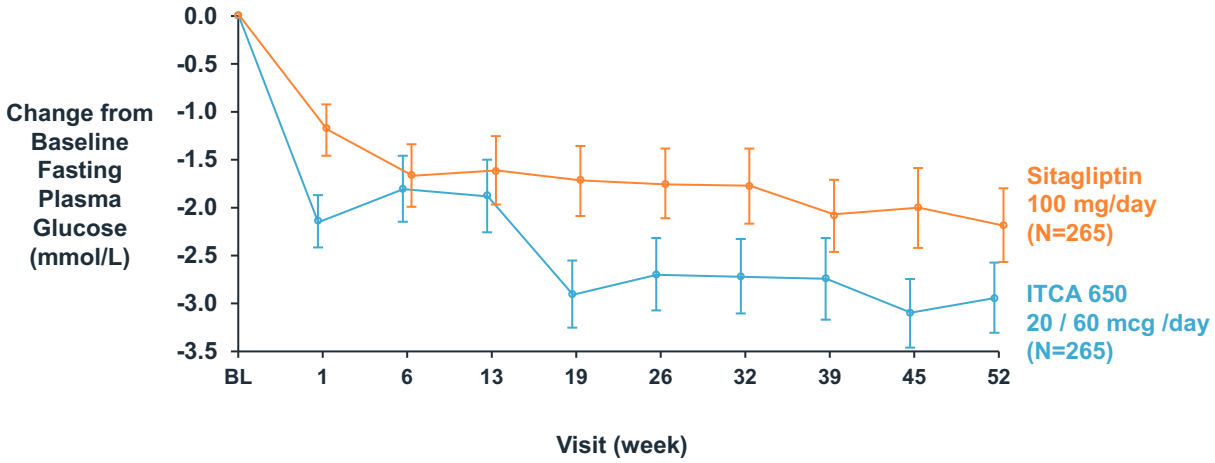
Intarcia Interval	Daily Range (mcg)	% of 60 mcg Target Range
0-14 Days	30 – 70	50 – 117%
14-28 Days	51 – 77	85 – 125%
28-42 Days	46 – 73	76 – 122%
70-84 Days	46 – 73	
126-140 Days	46 – 73	
168-182 Days	46 – 73	

8.4.3 Extensive Clinical Data Validate the IVR Upper and Lower Limits As Effective & Safe For The Intended And Labeled Use

The substantial clinical evidence shows that ITCA 650 is highly effective, and with a safety profile squarely in line with exenatide and GLP-1 products which all have labeled AKI Warning that outline an association with transient GI AEs during dose initiation and escalation along with other concomitant risk factors. There is nothing fundamentally new or different about ITCA 650 in this regard.

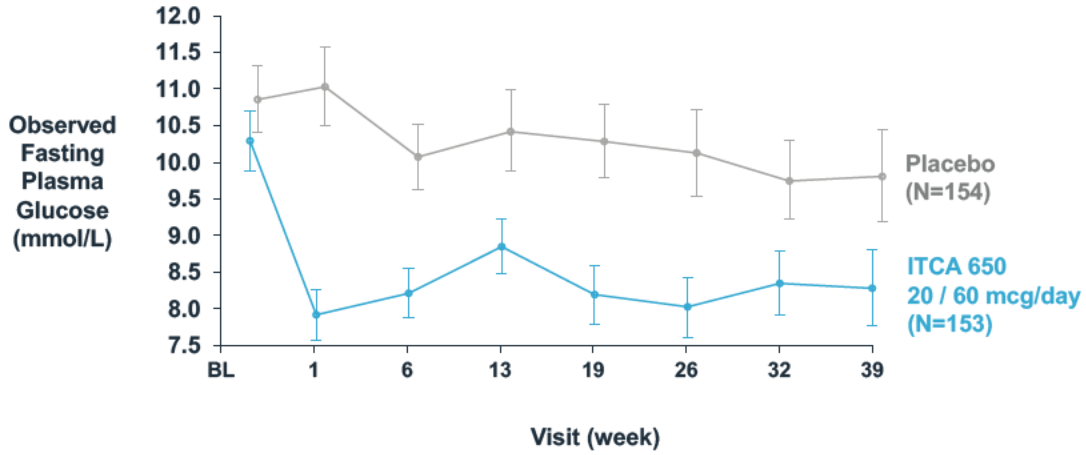
The totality of Phase 2 and Phase 3 shows unequivocal efficacy and safety data support the conclusion that ITCA 650 functions as designed and performs well for its intended use, having demonstrated sustained HbA_{1c} lowering and a GI AE and tolerability profile consistent with approved GLP-1s. In addition to the substantial HbA1c efficacy presented earlier, the Phase 3 fasting plasma glucose (FPG) data in Study 105 (Figure 35) and Study 103 (Figure 36) shows that 3- and 6-month devices performed continuously and effectively for the full use durations as designed.

Figure 35: Phase 3 Change from Baseline Fasting Plasma Glucose During Treatment Period (Study 105)



Mean (±2 SE) Change from Baseline FPG During Treatment Period

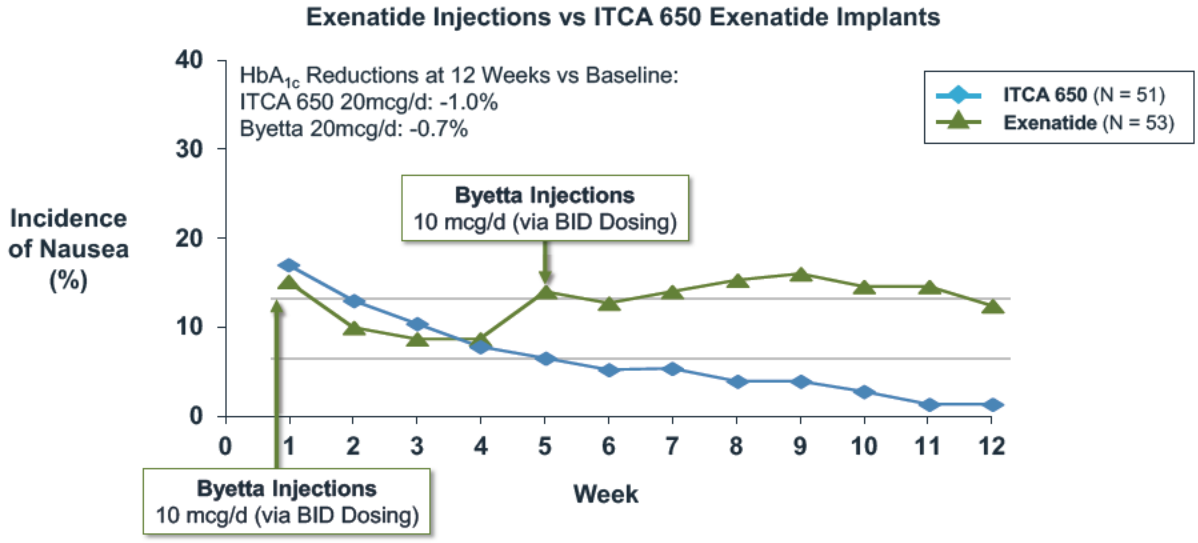
Figure 36: Phase 3 Change from Baseline Fasting Plasma Glucose During Treatment Period (Study 103)



Mean (±2 SE) Change from Baseline FPG During Treatment Period;
ITCA 650 40 mcg/day dose not shown

Since GI AEs are associated with AKI risk for the class at dose initiation, it is important to note that Intarcia ran a head-to-head Phase 2 trial against the only approved exenatide injectable product on the market at the time (Byetta). The results showed a markedly improved tolerability of ITA 650 implants over the 12-week dose initiation period, along with better glucose lowering efficacy (Figure 37). This study helped define the starting and maintenance doses for the Phase 3 program that were carried out successfully in all 4 Phase 3 RCTs.

Figure 37: Exenatide Injections vs ITCA 650 Exenatide Implants



BID: twice daily
Source: ITCA 650 Phase 2 Trial Done to Confirm Comparative Tolerability and Efficacy of Exenatide at the Same 20 mcg/day Starting Dose For 12 Weeks

In extensive Phase 3 trials with thousands of ITCA 650 3- and 6-month implants, the GI AE profile is squarely in-line with what is known for exenatide and approved GLP-1 products on the market (Figure 22 and Table 17).

8.4.4 PK/PD Profile Demonstrates Consistency of Exposure Comparable to Bydureon

Device reliability and consistency is also demonstrated by the clinical pharmacokinetic (PK) data in the NDA. The Phase 3 PK data are consistent and adequate, including a dedicated PK study (Study 109) performed in patients with renal impairment. Using the same assay across all Phase 1, Phase 2, and Phase 3 samples, the PK data demonstrated the consistency of steady-state exposures across the program and in patients across the Phase 3 trials using the Phase 3 devices.

In comparing ITCA 650 to other exenatide products, the most logical comparator is Bydureon for 3 reasons:

- Bydureon and ITCA 650 share similar design objectives. Both are extended-release products designed to give prolonged and continuous subcutaneous delivery of exenatide. Byetta is an aqueous solution dosed twice daily as an immediate-release formulation.
- Release profiles are similar. Both products give an early release of exenatide upon injection or placement, which results from absorption of exenatide that becomes immediately available to subdermal tissues. Initial exenatide concentrations from this early release decline over the subsequent hours, after which concentrations begin to increase as exenatide is released through the intended mechanism of each product. Steady state is reached for both delivery systems within several weeks, albeit more quickly for ITCA 650 than for Bydureon.
- Bydureon is approved for use in the United States and has a 7-year (since 27 Jan 2012) record of safety and effectiveness that provides relevant clinical context for evaluation of any safety- and efficacy-related effects of the PK characteristics described in the preceding two bullet points.

The initial peak in exenatide concentration that occurs when Bydureon is injected is analogous to the early release that can occur upon placement of ITCA 650. The specific mechanisms causing the peaks differ, but in both cases the initial peak represents absorption of exenatide that is immediately available upon injection or placement in a patient who has not yet become acclimated to exenatide. The initial release produces measurable exenatide concentrations in plasma, but they typically do not exceed subsequent steady-state concentrations. Because the peak is transient, occurring only in the hours after placement or injection, it is not known to what extent it may contribute to the higher rate of GI AEs reported within the first week after the first placement of ITCA 650, within the first week after ITCA 650 dose escalation, and within the first few weeks after starting Bydureon treatment (Horowitz 2017).

Table 34 compares the PK variability estimates that are publicly available for Bydureon to analogous estimates for ITCA 650. Between-subject variabilities for ITCA 650 are comparable to or lower than those for Bydureon, while the within-subject variability estimated by population PK analysis is 47% lower for ITCA 650 than for Bydureon (29% vs 55%, respectively).

Table 34: Comparison of Publicly Available Variability Estimates for Bydureon and the Analogous Estimate for ITCA 650

Variability Parameter	ITCA 650	Bydureon
Early release upon placement or injection	Yes	Yes
Within-subject CV		
Average Css over 24 hours	38%[a]	NA
Individual concentrations over 24 hours	65%[b]	NA
Between-subject CV		
Average Css	48%, 67%[c]	84%[d]
Individual concentrations	70%[e]	NA
Variability from the population PK model		
Within-subject	29%	55%[f]
Between-subject	41%	44%[f]

NA: not available; NC: not calculable

a This is within-subject CV in 24-hour CL/F in Study 109

b This is within-subject CV in individual concentrations over 24 hours in Study 109

c The estimate of 48% is the between-subject CV in 24-hour CL/F over a 4-fold range of eGFR Study 109. The estimate of 67% is the between-patient CV in average Css in Study 103 HBL Ext 1.

d This is between-patient variability in average Css in Bydureon Study BCB108, deduced to have been calculated as CV = standard deviation / mean.

e This is between-patient variability in individual concentrations in Study 103 HBL Ext 1.

f The variability of Bydureon estimated by the population PK analysis was reported as “the estimated variability of predicted steady-state exenatide concentration” between and within subjects, and was 44.2% and 54.8%, respectively. The publicly available information do not indicate whether these CVs reflect the Css in individual samples or the Css averaged across multiple samples.

The comparisons between Bydureon and ITCA 650 show that the overall PK characteristics and variabilities associated with the 2 products are generally comparable. Bydureon and ITCA 650 deliver the same drug in an extended-release manner. Bydureon and ITCA 650 both immediately release a small amount of exenatide upon injection or placement, which may produce pharmacologically active exenatide concentrations within a few hours after injection or placement. For both products, the initial peak is short-lived due to exenatide’s short half-life. The plasma concentration of exenatide can remain low for a few days after the early release is eliminated, as the microspheres or the mini-pump hydrate and begin to function and release exenatide as designed. Both products attain pharmacologically active exenatide concentrations and/or steady-state concentrations within a few weeks, after which exenatide

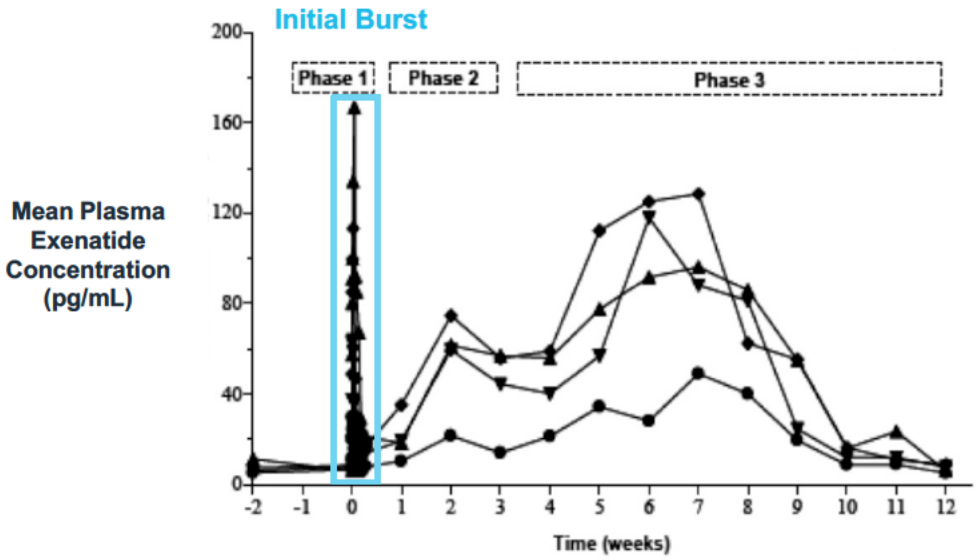
concentrations vary around their average steady-state levels until treatment is discontinued (for Bydureon or ITCA 650) or until the mini-pump is replaced (for ITCA 650).

These similarities in PK behavior and variabilities suggest that the safety and efficacy of ITCA 650 treatment should be similar to the safety and efficacy of Bydureon treatment.

Figure 38 shows the mean exenatide concentration over time following a single 2 mg dose of exenatide once weekly in patients with T2DM (n = 41). Figure **39** presents plasma exenatide concentrations (means ± SD) over time in patients receiving exenatide (n = 31).

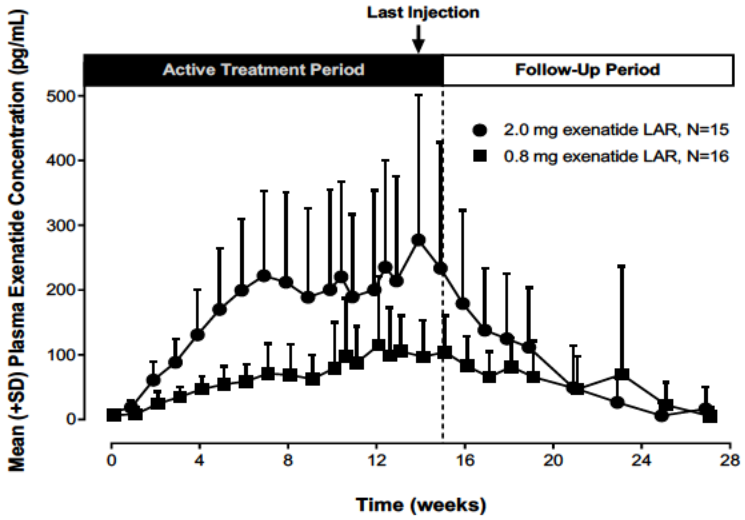
These figures demonstrate the multiphasic release of exenatide, with an initial period representing rapid release of surface bound exenatide followed by a gradual release and 2 subsequent peaks.

Figure 38: Bydureon's Tri-Phasic Depot Delivery System – An Initial Burst, Followed by PK Variability



Mean exenatide concentration over time following single dose of exenatide once weekly in patients with T2DM (n = 41).
Bydureon dose: 2 mg exenatide extended-release for injectable suspension
Source: FDA review:
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000ClinPharmR.pdf. Page 16

Figure 39: Bydureon's Tri-Phasic Depot Exenatide Delivery System - Significant PK Variability Is Observed and Inherent No Matter How Delivered



Source: Kim et al., Diabetes Care, 2007 Figure 2

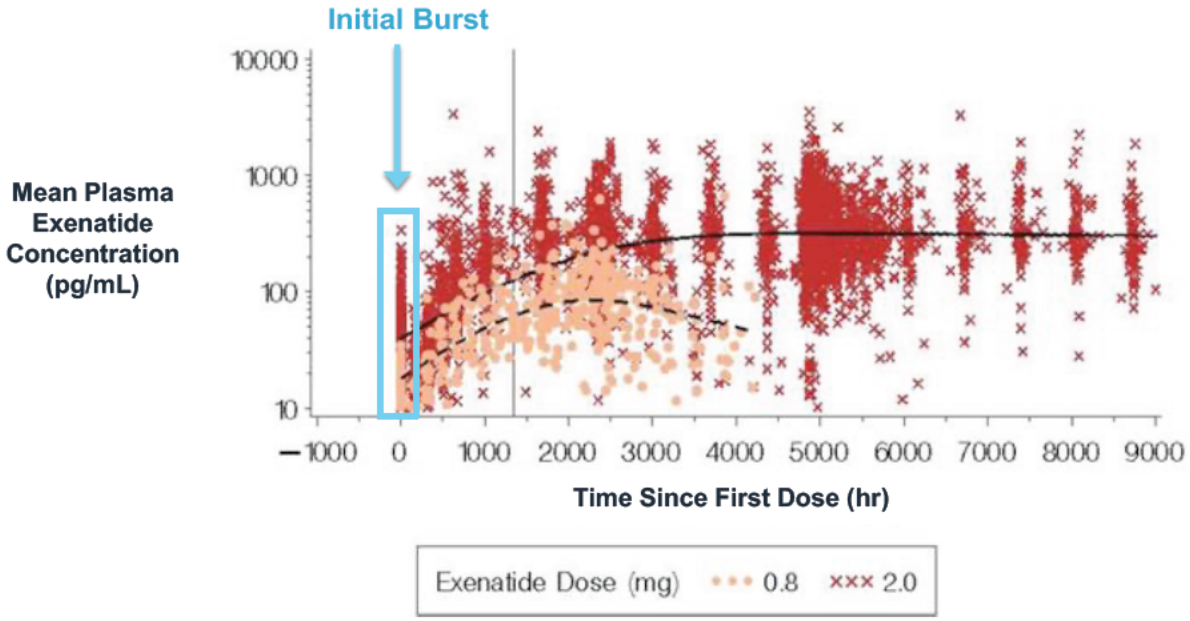
Note that the last injection was administered at Week 14.

FDA Clin Pharm Review: "A single dose of Bydureon exhibits multiphasic release of exenatide over approximately 10 weeks, with an initial period representing rapid release of surface bound exenatide followed by a gradual release and 2 subsequent peaks at around Week 2 and Week 6–7, respectively, representing the hydration and erosion of the microspheres."

Source for quote: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000ClinPharmR.pdf. Page 15

Given Bydureon's release behavior and PK profile, the exenatide concentration in plasma at any given time after reaching steady-state reflects the combined contribution of the previous 10 doses, although not all 10 doses contribute equally to the concentration at that time. Despite the fact that each steady-state plasma concentration represents the sum of contributions distributed over 10 weekly injections, the total variability in exenatide concentrations is substantial (Figure 40).

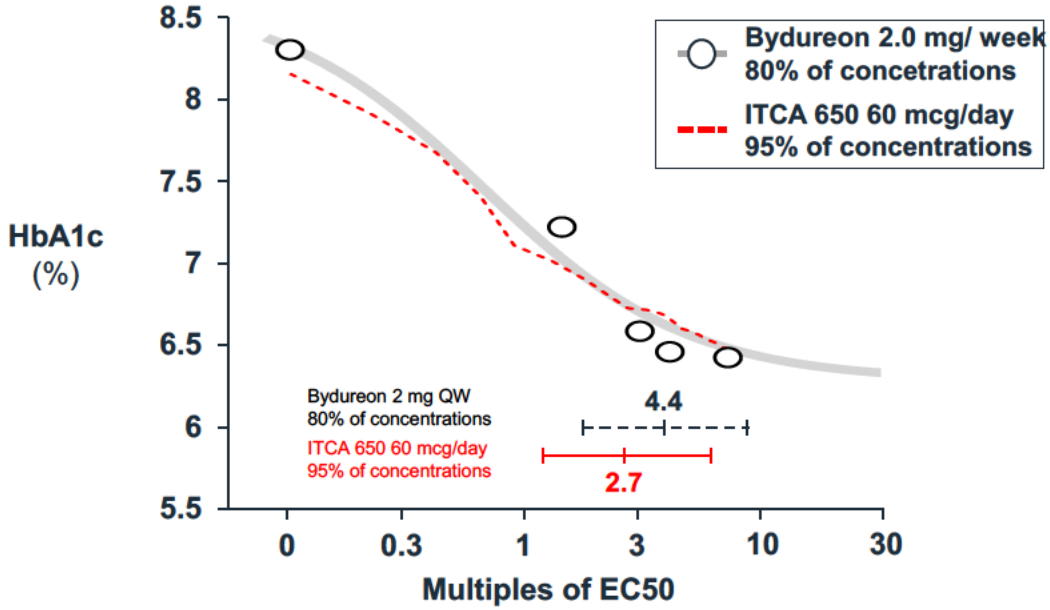
Figure 40: Bydureon PK (Exenatide) Variability: Initial Burst from Tri-Phasic Depot Delivery Followed by Significant PK Variability Inherent in Exenatide



Source: Cirincione B, Passarell J, Kothare P et al., poster at ASCPT 2009.

ITCA 650 PK/PD data demonstrated the consistency of steady-state exposures in patients across the Phase 3 trials using the Phase 3 devices. When comparing to approved exenatide products, the variability in exposure is less for ITCA 650 (Figure 41). To accommodate potential differences in exenatide assays, reported exenatide concentrations for Bydureon and ITCA 650 were expressed as multiples of their respective EC_{50}, a common unit of bioactivity. The bars below the curves represent the middle 80% of concentrations for Bydureon 2 mg once-weekly and the middle 95% of concentrations for 60 mcg/day ITCA 650. Compared to Bydureon 2.0 mg/week, ITCA 650 60 mcg/day is less variable. This holds true when comparing exposures to Byetta as well.

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



Data were derived by digitizing the plots of HbA_{1c} vs concentration in NDA Figure 2.7.2-37 and dividing the concentrations by the respective EC_{50} for ITCA 650 (126 pg/mL) and Bydureon (83.5 pg/mL). The gray curve is the best-fitting 3-parameter sigmoid for the Bydureon data.

Original source for Bydureon data:
https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/022200Orig1s000ClinPharmR.pdf (pg 9 of 44, Figure 3).

9 POST-MARKETING PLAN

9.1 Post-Approval CVOT Design Overview

Intarcia is committed to conducting a post-approval CVOT to demonstrate the cardiovascular safety and potential benefit of ITCA 650 and to confirm that proactive AKI SAE risk mitigations are effective.

Definitive plans for this trial will be agreed upon with the FDA prior to finalization. The main objectives and considerations are below.

- Objectives:
  - Primary: CV risk and benefit
  - Secondary: Initial renal safety and LT renal composite outcomes
- Comparator:
  - Placebo
- Patient population:
  - adult patients with T2DM and ~90% CV disease
  - ~15-20% of patients classified as elderly
  - ~30% of patients with renal impairment (eGFR aligned with label)
- Other:
  - ~1000 events
  - ≥ 3 years of exposure (maximum 3.5 years)
  - Sufficient sites for enrollment/completion goals

10 BENEFIT-RISK CONCLUSIONS

ITCA 650 has favorable benefit-risk comparable to GLP-l RAs based on the facts:

- ITCA 650 had unequivocal efficacy in all 4 RCTs, and a safety profile consistent with GLP-1s with labeled AKI Warnings associated with GI AEs (a class effect)
- ITCA 650 has the only twice-yearly maintenance dosing option that can help address widespread and longstanding poor glucose control and poor adherence that has not improved in the US in the last 15 years in > 50% of patients at risk
- ITCA 650 GI AEs at dose initiation/escalation are an established risk factor for pre-renal AKIs in multiple GLP-1 CVOTs and numerous post-marketing reports
    - ITCA 650 should be granted class-labeled AKI Warnings as all the same known AKI risk factors and mitigations in GLP-1 AKI Warnings apply
- ITCA 650 should be granted post-approval CVOT, having met the pre-approval primary endpoint required to bridge to a larger/longer post approval CVOT

No other available therapy in the class offers certain patient in need the remarkable option of once-every-six-month maintenance dosing that a doctor would now be able to administer just twice-yearly- when glucose control and known adherence issues exist.

New maintenance therapy options and patient/provider choice are very important benefit/risk considerations and ITCA 650 is a distinct new option for patients that addresses the exact concerns that have been raised by patients, providers, and the preeminent voices in the field in support of ITCA 650.

11 DEVICE / CMC RELATED REQUESTS ON ISSUES 4–6 - EACH PREVIOUSLY ADDRESSED BY FACTS ON RECORD

11.1 Issue #4: Device Failure Risk Identification and Mitigation

11.1.1 Overview

The issues regarding device failure risk and responses on record are outlined below. Improvements to QA/QC controls based on FDA feedback have resulted in low ITCA 650 failure rates. If a failure were to occur, it would be readily identified through biological symptoms such as increases in blood glucose or GI AEs.

Table 35 provides the facts that systematically addresses each concern for this issue.

Supporting analyses and data are provided after the table.

Table 35: Summary of Issue 4 (Device Failure Risk) Identification and Mitigations); Key Facts on Record

Verbatim Issue	Key Facts
Variability in the daily in vitro drug-release data did not support the use of weekly and biweekly averages to calculate device failure rates.	• **The average delivery rates were comparable between daily and weekly/biweekly IVR measurements.** • **The one-time daily IVR study met all acceptance criteria when applying pre-specified testing intervals and limits.** • **Importantly, extensive Phase 3 clinical and registration lots met the weekly and bi-weekly pre-specified IVR upper and lower limit specifications and are validated as highly effective and safe for the intended and labeled use**

The failure rate data was inadequate to support the safety and effectiveness of the device constituent of ITCA 650.	• **The noted failure rate raised in this issue is 1.46% for devices earlier in the development program. After DFMEA work the device failure risks were identified and mitigated to only 0.26% overall (and on the 3 individual components between 0.0% and 0.17%).**
	• **ITCA 650 devices performed as designed to deliver exenatide for the full duration of use and within the established IVR specifications, as evidenced by**
	  ○ **The totality of the successful clinical trials data and overall benefit/risk profile**
	  ○ **Extensive in vitro performance testing on clinical and registration drugs lot employed in the program that met IVR specifications**

The sponsor provided inadequate mitigation strategies to reduce device failures.	• **Mitigation strategies used by Intarcia are effective given the facts noted, and the current device failure rates are very low.** • **Moving from manual manufacturing processes to automated manufacturing played a role in achieving these very low rates as well.**

DFMEA: design failure mode and effect analysis; IVR: in vitro release

11.1.2 Failure Rate and Mitigation

As discussed in Section 3.4.2.1, the cited cumulative failure rate of 1.46% for the 60 mcg/day product is based on early development stage data provided in the NDA, before DFMEA work and mitigations were applied (Table 36). As with the life cycle of any device, ITCA 650 failure was assessed per DFMEA regulations to identify, quantify, and mitigate failure. Through the revised mitigation steps, the initial failure rate was brought down to less than 0.26% prior to the NDA resubmission and CRL 2; these data have already been submitted and should have replaced the 1.46%.

Table 36: Post-DFMEA Mitigations

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

DFMEA: design failure mode and effect analysis

11.2 Issue #5: Assurance of Sterility

11.2.1 Overview of Factual Errors

The issues regarding assurance of sterility are outlined below. All sterility testing met acceptance criteria for sterility and integrity of the container-closure system and all FDA requests have been fulfilled.

Table 37 provides the facts that systematically addresses each concern for this issue.

Supporting analyses and data are provided after the table.

Table 37: Summary of Issue 5 (Sterility) and Key Facts on Record

Verbatim Issue	Key Facts
The container-closure integrity test data provided to support integrity of a container-closure system used for sterile intermediate storage of sterile components of ITCA 650 was inadequate.	• **Container-closure integrity test (CCIT) met all acceptance criteria and provided high degree of assurance of maintaining the sterile barrier.** • **Intarcia responded to IR on 19 December 2019 (SEQ0062) and March CRL emphasizing that the CCIT testing met the acceptance criteria and sterility of the barrier was assured.**
Information regarding the product-contact filling equipment used for commercial manufacturing of ITCA 650 was inadequate in support of sterility assurance for ITCA 650.	• **In CRL, the Division referred to an alternate filling head in err; however, the planned future change discussed in the PAI concerned the filler manifold. A permitted change being planned for post-approval commercial scale up activities but not relevant to the NDA review.** • **The new filler manifold had not been used for any cGMP manufacture of ITCA 650; At the request of the FDA we performed another sterility test (PST) with the original filler manifold and documented to FDA it was successful.**
Information provided to support the routine depyrogenation process for components of the primary container-closure system for ITCA 650 was inadequate in support of sterility assurance for ITCA 650.	• **Process for components of primary container-closure system provided to FDA on 12/19/2019 and 11/25/2020.** • **No concerns raised or any 483 observations during 1/2020 Pre-Approval Inspection (PAI).**
The method suitability data provided to support the proposed routine endotoxins test method with ITCA 650 was inadequate in support of sterility assurance for ITCA 650.	• **Data to support the proposed routine endotoxins test method with ITCA 650 was shared during the PAI and in subsequent communication with CDER.** • **Intarcia submitted enhanced bacterial endotoxin test method to the FDA on 06 January 2020 (SEQ0063) and provided additional details and documentation to the FDA in communication on 30 January 2020 (SEQ0066) and in response to Form FDA 483 observations on 03 February 2020.** • **2020 Pre-Approval Inspection report from FDA confirms that test method validation was in progress and completed during the inspection, with Intarcia providing documented data showing all criteria were successfully met.**

CDER: Center for Drug Evaluation and Research; cGMP: current good manufacturing practices; CRL: complete response letter; FDA: Food and Drug Administration; IR: information request

11.2.2 Sterility Concern at Third Party Testing Lab Were Previously Addressed

The sterility concern raised stems in part from a one-time Out-of-Specification (OOS) sterility test in a third-party lab in August 2017 that led to a clinical hold. This is based on obsolete information and has been previously addressed. The OOS result related to two lots of ITCA 650 that were produced a year apart and were undergoing stability testing in the lab. Intarcia and the related contract testing laboratory, Catalent Pharma Solutions (Catalent), conducted investigations into the OOS results. Both concluded that a laboratory error (lack of sterile barrier integrity found in 3 of 6 sterility test isolator gloves in a newly installed isolator at Catalent) was the probable cause of the sterility OOS results. Once the isolator gloves were replaced, sterility testing resumed successfully.

Out of an abundance of caution, Intarcia also implemented comprehensive Corrective Actions and Preventative Actions (CAPA) in response to the OOS results. The Intarcia Sterility Assurance Plan, VV 54514, documents the controls, validations, and monitoring currently in place to provide sterility assurance. The plan also summarizes significant manufacturing and 3rd party testing improvements since the OOS results occurred. These improvements were shared with the FDA investigators during the PAI and submitted to FDA on 3 February 2020.

Intarcia has provided a detailed description of the sterility investigations and related CAPA to FDA. The specific sterility issues identified have been previously addressed and this is confirmed by the lead FDA inspector during the 2020 PAI inspection at Intarcia's manufacturing site. In his Establishment Inspection Report, it is noted that all sterility and related data in this matter were comprehensively reviewed and that there were no deficiencies remaining.

11.3 Issue #6: Demonstration of Quality Controls

11.3.1 Inaccurate Representation of Insufficient Demonstration of Quality Controls

The issues raised and previously addressed regarding quality controls are outlined below. There is no evidence of empty devices in the thousands of implants tested via IVR or in any of the thousands of devices that performed successfully in all 4 RCTs.

All site PSTs (sterility tests) conducted relating to manufacturing ITCA 650 passed and are on record. The quality is also supported by the unequivocal and consistent efficacy and safety observed across all 4 of the ITCA 650 randomized clinical studies showing similar efficacy and a safety profile that is squarely in-line with other GLP-1s that are also labeled for AKI Warnings associated with GI AEs during dose initiation and escalation.

Table 38 provides the facts that systematically addresses each concern for this issue.

Table 38: Summary of Issue 6 (Quality Controls) and Key Facts on Record

Verbatim Issue	Key Facts
Controls were inadequate to ensure empty devices would not be included in the final release of ITCA 650.	• **Intarcia has always implemented robust filling controls to prevent the release of empty devices, as well as a final X-ray inspection process on all finished products.** ○ **No empty system has been detected among > 3,000 devices tested during IVR studies; these data have been provided to the FDA.** • **There were no product complaints related to the thousands of devices used in Phase 3 and the efficacy data in all 4 RCTs. This information has been provided to the FDA.** • **The Post-Application Action Letter response, as well as the responses to the 483, fully address the inspectional issues.**

Qualification of the filling line with an original or new manifold was not performed.	• **The new manifold has not been qualified because it has not been implemented yet; it is a future change for post-approval commercial scale up and it will be qualified and well documented per standard procedures/requirements.**
	• **Issues of qualification of the filling line with the original manifold have been previously addressed.**
	  ○ **Intarcia successfully completed an additional process simulation test (PST) for use of the original filler manifold.**
	  ○ **In the 5 March 2020 letter to FDA, Intarcia informed the Agency that the additional PST was successfully completed and met acceptance criteria.**

The results and reports of the process simulation test, used to demonstrate the effectiveness of preventing microbiological contamination of ITCA 650, were not provided	• **Intarcia provided the results of all PSTs conducted to the Agency during the PAI. All PSTs successfully met acceptance criteria.**

FDA: Food and Drug Administration; IVR: in vitro release; PAI: pre-approval inspection; RCTs: randomized clinical trials; PST:

11.4 Conclusions

Based on the corrected facts, again summarized in Table 39, and to align with precedent for approved GLP-1s, ITCA 650 should be approved with the labeled AKI Warnings and risk mitigation measures commensurate with the GLP-1 RA class and a commitment for a post-approval CVOT.

Table 39: Summary of Claimed Issue and Substantial Factual Errors

Claimed Issue	Conclusions Based on Substantive Facts & Guidance
Device Failure Risk	• Device failure risks identified and mitigated to very low level of 0.26% • Any rare failures can be readily identified through biological symptoms
Sterility	• FDA information requests regarding sterility all responded to / previously addressed on record. • No sterility issues documented in FDA EIR report
Device quality controls	• No empty devices detected during IVR studies (n > 3,000) or for RCTs (n > 22,000) • All site PSTs (sterility tests) passed and are on record

EIR: Establish FDA: Food and Drug Administration; IVR: in vitro release' PSTs: process simulation tests; RCTs: randomized clinical trials

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13 APPENDICES

13.1 Independent Expert Evaluation and Report of AKI SAEs in Study 107

SERIOUS AKI CASE SUMMARIES & EXPERT CAUSALITY ASSESSMENTS – STUDY 107 (CVOT)

13.1.1 Executive Summary

Intarcia acknowledges the numerical imbalance in serious AKI cases reported in our pre-approval cardiovascular outcomes trial (CVOT), Study 107. Intarcia has undertaken a thorough review of all relevant safety data generated in Study 107, engaging both internal and external experts to review all available data (including appropriate source documents) related to the serious AKI cases observed in Study 107, and to make a causality assessment based on the WHO-UMC system for standardized case causality (WHO-UMC). In addition, determinations were made whether cases were considered certainly, probably, or possibly related to drug, as well as whether they were consistent with class labeling for the GLP-1 receptor agonists (Table 40).

When combining drug and placebo, 17 serious AKI events were reported in patients in Study 107. Two were non-treatment-emergent (defined in protocol as occurring any time prior to first device placement or after the last device removal). Eleven (0.5%) were treatment-emergent in ITCA 650-treated patients vs 4 (0.2%) in placebo-treated patients. Important details for these AKI cases are concisely displayed in Table 40, and individual case narratives providing additional detail are listed afterwards.

Of the 11 ITCA 650 treatment-emergent cases, 8 (0.4%) were determined by the expert panel to be probably or possibly related to treatment, despite the presence of other potential contributing risk factors such as underlying renal impairment at baseline and pre-existing use of one or more concomitant medications (i.e., metformin, diuretics, ACE/ARBs, NSAIDS) known to increase the risk of dehydration and renal dysfunction on their own.

Of the 8 treatment-emergent cases, 6 were considered probable while 2 were considered possibly related to treatment:

- Four of the 6 probable cases (107-001, 107-002, 107-003, and 107-004) occurred within 19 days after placement of a treatment initiation device (20 mcg daily). All patients experienced mild-to-moderate GI AEs preceding identification of AKI. Three of the 4 patients were also taking concomitant medications (metformin, diuretic, NSAID, ACE-inhibitor), which may have contributed to volume depletion. All patients recovered and 2 of the 4 discontinued treatment.

- Two of the 6 probable cases occurred 17 days (107-005) and 30 days (107-006) after placement of the first escalation device (60 mcg daily) after ~ 3 months on the low dose device. Patient 107-006 experienced severe diarrhea and dehydration upon diagnosis of acute renal failure. The patient was also on concomitant metformin, diuretics, and an ACE inhibitor. Patient 107-005 was on metformin and started on both losartan and rosuvastatin the same day that the 60-mcg device was placed and experienced mild vomiting. The patient also experienced moderate dehydration upon admittance to the hospital. Both patients recovered with patient 107-005 continuing treatment.

- One of the 2 possible cases (107-007) occurred within 75 days of the 20 mcg starting dose device while the other case (107-008) occurred following placement of the third consecutive 60 mcg device (Day 559). Patient 107-007 experienced moderate GI AEs within 5 days leading to moderate dehydration and AKI. This initial event was followed by waxing and waning deterioration of renal function with no further AKI events. Patient 107-008 experienced nausea and vomiting approximately 15 days prior to the event with diarrhea and acute gastroenteritis 2 days prior to the event. Both patients recovered, with patient 107-007 continuing treatment.

The expert review identified 3 ITCA 650-treated serious cases that were considered unlikely related to treatment for the reasons noted in the bullet points listed below:

- Patient 107-009 experienced post-operative bleeding requiring transfusion with documented hypotension, while on warfarin. There were no concurrent GI symptoms.
- Patient 107-010 had acute onset of nausea and vomiting that developed immediately following the ingestion of antibiotics and pain medications on an empty stomach.
- Patient 107-011 was hospitalized on Day 281 after new onset of nausea, vomiting and diarrhea after initiating antibiotic therapy for a UTI. The patient was also self-treating with multiple (3) NSAIDs.

Finally, the expert review also identified 2 ITCA 650-treated serious cases that were assessed as not being treatment-emergent when details regarding the timing of onset and initiation or cessation of treatment with ICTA 650 were discerned more closely.

- The first AKI case (107-012) was assessed as not treatment-emergent per protocol because the patient had onset of AKI approximately 6 weeks after ITCA 650 removal. There were also no associated GI symptoms.

The second AKI case (107-013) involved a patient that just prior to the first device placement progressed to renal status to Stage 3A moderate renal failure compared to

screening labs obtained 3 weeks earlier. Per protocol this event was prior to device placement and no GI AEs were noted prior to or after the start of ITCA 650. The patients recovered while on therapy and finished the trial.

SERIOUS AKI CASE SUMMARIES AND CAUSALITY ASSESSMENTS – STUDY 107

CAUSALITY CRITERIA

Sponsor assessment of causality is based on the causality categories described by the Uppsala Monitoring Centre, as follows:

1. *Certain:* a clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.

2. *Probable/Likely:* a clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.

3. *Possible:* a clinical event, including laboratory test abnormality, with a reasonable time sequence to administrations of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.

4. *Unlikely:* a clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

GLP-1 RA Class Labeling/Warning For AKI. We have considered that a case “fits pattern for AKI as shown in GLP-1 RA class labeling” when it is in accordance with the text approved for Bydureon USPI, Warnings, Section 5.4 on Acute Kidney Injury and Impairment of Renal Function: “Some of these events occurred in patients receiving one or more pharmacologic agents known to affect renal function or hydration status such as angiotensin converting enzyme inhibitors, nonsteroidal anti-inflammatory drugs, or diuretics. Some events occurred in patients who had been experiencing nausea, vomiting, or diarrhea, with or without dehydration.”

Table 40: Serious AKI Case Summaries & Causality Assessments – Study CLP-107 Overview

Patient	Baseline eGFR; Renal Staging**	Dose and Study Day at onset of AKI	Relationship	Discontinued Rx	AKI Resolved	AKI Resulting in Death or Dialysis	GI Event: Severity***	KDIGO Grade: 0, 1, 2 or 3****
107-001	63 mL/min; Mild (Grade 2)	20 mcg Day 7[a]	Probable	N	Y	N	Nausea: Mild Diarrhea: Mild Vomiting; Unknown Severity	Grade 3 Baseline SCr: 1.13 mg/dL SCr ~AKI: 3.8 mg/dL
107-002	68 mL/min; Mild (Grade 2)	20 mcg Day 19 [a]	Probable	Y	Y	N	Nausea: Unknown Severity Vomiting: Moderate Diarrhea: Unknown Severity Dehydration: Moderate	Grade 3 Baseline SCr: 1.08 mg/dL SCr ~AKI: 3.6 mg/dL
107-003	62 mL/min Mild (Grade 2)	20 mcg Day 8 [a]	Probable	N	Y	N	Nausea: Moderate Vomiting: Moderate Diarrhea: Moderate	Grade 2 Baseline SCr: 1.15 mg/dL SCr ~AKI: 3.0 mg/dL
107-004	87 mL/min @ Screening Mild (Grade 2) @ Screening	20 mcg Day 8 [a]	Probable	Y	Y	N	Nausea: Mild Vomiting: Mild	Grade 3 Baseline SCr: 0.9 mg/dL

Patient	Baseline eGFR; Renal Staging**	Dose and Study Day at onset of AKI	Relationship	Discontinued Rx	AKI Resolved	AKI Resulting in Death or Dialysis	GI Event: Severity***	KDIGO Grade: 0, 1, 2 or 3****
								SCr ~AKI: 4.2 mg/dL
107-006	62 mL/min Mild (Grade 2)	60 mcg Day 117 [a]	Probable	Y	Y	N	Diarrhea: Severe Dehydration: Severe	Grade 2 Baseline SCr: 1.15 mg/dL SCr ~AKI: 2.3 mg/dL
107-005	48 mL/min Moderate (Grade 3a)	60 mcg Day 111 [a]	Probable	N	Y	N	Vomiting: Mild Dehydration: Moderate	Grade 1 Baseline SCr: 1.6 mg/dL SCr ~AKI: 2.6 mg/dL
107-007	57 mL/min Moderate (Grade 3a)	20 mcg Day 75	Possible	Y	Y, with sequalae	N	Nausea: Moderate Vomiting: Moderate Diarrhea: Moderate Dehydration: Moderate	Grade 1 Baseline SCr: 0.97 mg/dL SCr ~AKI: 1.89 mg/dL
107-008	83 mL/min Mild (Grade 2)	60 mcg Day 559	Possible	N	Y	Y (Short term dialysis)	Late/intermittent GI AEs; on day 559, Unknown severity Nausea: Unknown	Grade 3 Baseline SCr: 0.71 mg/dL SCr ~AKI: 9.26 mg/dL

Patient	Baseline eGFR; Renal Staging**	Dose and Study Day at onset of AKI	Relationship	Discontinued Rx	AKI Resolved	AKI Resulting in Death or Dialysis	GI Event: Severity***	KDIGO Grade: 0, 1, 2 or 3****
							Severity Vomiting: Unknown Severity Diarrhea: Unknown Severity	
107-009	58 mL/min Moderate (Grade 3a)	60 mcg Day 500	Unlikely	N	Y	N	No GI Events Reported	Grade 2 Baseline SCr: 0.97 mg/dL SCr ~AKI: 2.6 mg/dL
107-010	50 mL/min Moderate (Grade 3a)	60 mcg Day 748	Unlikely	Y	Y	N	Nausea: Moderate to Severe to Moderate Vomiting: Moderate to Severe to Moderate Dehydration: Severe	Grade 0 Baseline SCr: 1.39 mg/dL SCr ~AKI: 1.7 mg/dL
107-011	64 mL/min Mild (Grade 2)	60 mcg Day 281	Unlikely	N	Y	N	Vomiting: Mild Diarrhea: Mild	Grade 3 Baseline SCr: 0.87 mg/dL SCr ~AKI: 3.0 mg/dL

Patient	Baseline eGFR; Renal Staging**	Dose and Study Day at onset of AKI	Relationship	Discontinued Rx	AKI Resolved	AKI Resulting in Death or Dialysis	GI Event: Severity***	KDIGO Grade: 0, 1, 2 or 3****
107-013*	63 mL/min Moderate (Grade 3a)	20 mcg Day 1	Non-Treatment-Emergent (AKI onset Day 1, prior to ITCA 650 placement)	N	Y	N	No GI Events Reported	Grade 1 Baseline SCr: 1.17 mg/dL SCr ~AKI: 1.8 mg/dL
107-012*	80 mL/min Mild (Grade 2)	60 mcg Day 312	Non-Treatment-Emergent (AKI onset 44 days post-ITCA removal)	Y (44 days prior to AKI event)	Y	N	Dehydration: Severe	Grade 0 Baseline SCr: 0.95 mg/dL SCr ~AKI: 1.41 mg/dL

13.1.2 Serious AKI Case Summaries & Causality Assessments – Study 107 Case Narratives

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function*	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Sponsor Assessment of Causality	Disposition
107-001	Day 7	20 mcg	MI, CABG, Hypertension, Sleep apnea, GERD, Barrett's esophagus, Smoker	Mild impairment	Volume Contraction due to mild nausea and diarrhea, and one day of vomiting	ARB, Diuretic	Yes; mild GI AEs + con meds	Probable	Recovered on Tx / Completed Tx
SUMMARY	**Preferred Term: Acute kidney injury (Verbatim: Acute kidney injury)** – 76-year-old Caucasian male (baseline eGFR 63 ml/min; BUN 23 mg/dL; creatinine 1.13 mg/dL) underwent a routine screening endoscopy on Study Day 2. Immediately following the procedure, the patient experienced 4 days of loose stools/watery diarrhea (every 30-60 min per patient), mild abdominal discomfort and nausea. No gastrointestinal bleeding or fresh blood per rectum was noted. On Study Day 7, the patient presented to the site with lightheadedness, dizziness, diarrhea and one day of vomiting; vital signs revealed a blood pressure of 63/40 mmHg and heart rate of 81 bpm. He was subsequently sent to the emergency room due to hypotension. In the ER, labs revealed an eGFR of 16 ml/min, increased BUN of 72 mg/dL and increased creatinine of 3.8 mg/dL, and the patient was admitted to the hospital for acute kidney injury (SAE, severe). CT scan of the abdomen and renal ultrasound were unremarkable. *Clostridium difficile* testing was negative. Treatment included IV fluids, ondansetron, metronidazole, and loperamide. On Study Day 8, creatinine had decreased to 1.6 mg/dL, BUN to 49 and eGFR had increased to 42 ml/min. On Study Day 9, AKI was considered resolved and the patient was discharged. Subsequent labs at the next scheduled visit (Study Day 85) were eGFR 80 ml/min, creatinine 0.92 mg/dL and BUN 24 mg/dL. The patient completed the study per protocol with no further GI events. **Intarcia assessment:** Volume contraction with 4 days of watery diarrhea, mild nausea, and one day of vomiting at presentation. Relationship between ITCA 650 and the GI events is probable; concomitant diuretic may have contributed to volume depletion that precipitated the AKI event.								

*Renal Function (based on eGFR):

Normal: ³ 90 mL/min

Mild impairment: 60 - < 90 mL/min

Moderate impairment: 30 - < 60 mL/min

Severe impairment: < 30 mL/min

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Sponsor Assessment of Causality	Disposition
107-002	Day 19	20 mcg	COPD, Hypertension, Former Smoker	Mild impairment	Volume loss due to Nausea, Vomiting and Diarrhea	NSAID, ACE-I Pancreatitis	Yes; moderate GI AEs + con meds + pancreatitis	Probable	Recovering following device discontinuation
SUMMARY	**Preferred Term: Renal failure (Verbatim: Renal failure)** – 67-year-old Caucasian male (baseline eGFR 68 ml/min; BUN 14 mg/dL; creatinine 1.08 mg/dL) developed persistent diarrhea, nausea, vomiting (non-serious, moderate) and dehydration (non-serious, moderate) on Study Day 3 and was hospitalized on Study Day 19. On admission, the patient reported 10-day history of nausea, vomiting and abdominal/epigastric pain that had increased over the weekend; on exam the patient was profoundly lightheaded and weak with significant dehydration, hypotension and tachycardia. Lipase and amylase were increased to 217 IU/L (0-59) and 116 IU/L (31-124), respectively and BUN and creatinine were elevated (63 mg/dL and 3.6 mg/dL respectively) with decreased eGFR (17 mL/min). CT scan of the abdomen and pelvis revealed no acute abnormalities; bilateral non-obstructive nephrolithiasis, renal cysts and sigmoid diverticulosis without diverticulitis were noted. The patient was diagnosed with acute pancreatitis (maximum lipase 437 IU/L on Study Day 20) and acute renal failure (SAE, severe). The patient was given nothing by mouth; lisinopril and metformin were discontinued. He was treated with aggressive IV fluid hydration and pantoprazole with subsequent resolution of acute renal failure and the GI symptoms. The ITCA 650 device was removed on study day 19 due to the AKI event. On study day 25, lipase had decreased to 86 IU/L, liver function tests were normal, BUN decreased to 15 mg/dL, creatinine decreased to 1.5 mg/dL and eGFR increased to 47 mL/min. On Study Day 27, the patient was discharged from the hospital. On Study Day 34, labs showed creatinine 1.1 mg/dL, BUN 15 mg/dL and eGFR >60 mL/min. **Intarcia Assessment:** Relationship between ITCA 650 and volume depletion secondary to nausea, vomiting, and diarrhea is probable, with acute pancreatitis (adjudicated as possible acute pancreatitis – atypical abdominal symptoms, non-severe) a likely contributing factor.								

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Sponsor Assessment of Causality	Disposition
107-003	Day 8	20 mcg	Chronic renal failure, Hypertension, Coronary bypass surgery, Former Smoker, Recurrent UTI	Mild impairment	Volume Depletion due to Nausea, Vomiting, Diarrhea and Reduced PO intake	None	Yes; Moderate GI AEs and reduced PO intake	Probable	Recovered on Tx / Completed Tx. No AKI following increase to 60 mcg
SUMMARY	**Preferred Term: Acute Kidney Injury (Verbatim: Acute Renal Failure)** – 73-year-old Caucasian male (baseline eGFR 62 ml/min; BUN 22 mg/dL; creatinine 1.15 mg/dL) developed nausea, vomiting, and diarrhea (non-serious AEs) on Study Day 6. On Study Day 8, the patient reported burning with urination and was prescribed cefuroxime for 2 days for a suspected UTI; and was diagnosed with AKI (SAE, moderate) the same day. On Study Day 10, the patient continued to report burning and pain with urination and developed a fever. He was treated with diclofenac (one dose only) for suspected urolithiasis. On Study Day 11, the patient reported he had no urine output and was subsequently hospitalized, with chief complaints of nausea, vomiting, diarrhea and decreased urine output. Labs at that time revealed creatinine 3.0 mg/dL and BUN 86 mg/dL. An ultrasound showed kidneys of normal size, and a CT scan showed right and left kidneys of normal size and shape without stones or hydronephrosis. Treatment included IV fluids, discontinuation of diclofenac, and temporary hold of metformin and glimepiride (Amaryl). Urine cultures showed no growth. The AKI event was considered resolved on Study Day 14 and the patient was discharged; creatinine was 1.4 mg/dL and BUN was 37 mg/dL. **Intarcia assessment:** Relationship between ITCA 650 treatment and precipitating events of nausea, vomiting, and diarrhea is considered probable.								

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Sponsor Assessment of Causality	Disposition
107-004	Day 8	20 mcg	Angina, Active Smoker, Hypertension	Mild impairment	Volume depletion due to nausea and vomiting (mild) and increase in furosemide dose	Three diuretics, ACE-I	Yes; mild GI AEs + con meds	Probable	Recovering at time of Tx discontinuation
SUMMARY	**Preferred Term: Renal Impairment (3 instances; Verbatim: Decreased Renal Function)** – 62-year-old Caucasian male with a history of coronary artery disease, hypertension, and peripheral edema. Screening labs (26 days prior to randomization) showed eGFR 87 ml/min, BUN 10 mg/dL and creatinine 0.9 mg/dL. Twelve days prior to randomization, the patient's furosemide dose was doubled (from 40mg QD to 40mg BID) for treatment of increased peripheral edema; the patient was also taking spironolactone 25 mg QD and hydrochlorothiazide 12.5 mg QD. On the day of initial ITCA 650 placement the patient developed mild nausea, anorexia and dizziness and his glimepiride was held. On Study Day 2, the patient developed mild vomiting. On Study Day 4, the patient was diagnosed with renal impairment (non-serious AE, moderate) with eGFR 29 ml/min, BUN 39 mg/dL, and creatinine 2.3 mg/dL, and he was noted to have decreased blood pressure and weight loss compared to baseline values. No anti-emetics were given at this time. On Study Day 8, eGFR was 14 ml/min and creatinine 4.2 mg/dL; renal impairment was upgraded to a SAE of moderate severity and the patient was hospitalized. Treatment included pantoprazole for nausea, 3 liters of IV fluids, and temporary suspension of furosemide, spironolactone, HCTZ, ACE-I, beta-blocker, calcium-channel blocker, statin and metformin. On Study Day 9, the vomiting resolved. ITCA 650 was discontinued on Study Day 10 due to the AKI event; at that time eGFR was 27 ml/min, BUN was 46 mg/dL, and creatinine was 2.5 mg/dL. On Study Day 11, symptoms of anorexia, nausea and emesis persisted; metformin was resumed at a lower dose after being held for the prior 3 days. On Study Day 12, renal impairment was downgraded to non-serious, remained moderate in severity, and the patient was discharged from the hospital (eGFR was 43 ml/min and creatinine 1.6 mg/dL). On study day 15, eGFR was 64 ml/min and creatinine 1.2 mg/dL; antihypertensive medications and diuretics were restarted (furosemide and beta blocker at lower doses then pre-event) and metformin was increased to baseline dose. The renal impairment was considered resolved on Study Day 15. On Study Day 45 (35 days after ITCA 650 removal), the nausea resolved. **Intarcia assessment:** While the relationship between ITCA 650 and GI events of nausea and vomiting is considered probable, the concomitant use of 3 diuretics, and particularly the doubling of the furosemide dose 12 days prior to ITCA 650 initiation, likely contributed to the patient's volume depletion and precipitation of the AKI event.								

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Sponsor Assessment of Causality	Disposition
107-006	Day 117	60 mcg	Hypertension, CHF, AAA, Ex-Smoker, CAD, Cardiac Stent, Sleep Apnea	Mild impairment	Volume loss due to diarrhea/ intermittent fecal incontinence	Diuretics, ACE-I, Nephrolithiasis	Yes; moderate -severe diarrhea + con meds	Probable	Recovered prior to Tx Discontinuation
SUMMARY	**Preferred Term: Acute prerenal failure (Verbatim: Acute renal failure related to prerenal factors)** – 74-year-old Caucasian male (baseline eGFR 62 ml/min; BUN 26 mg/dL; creatinine 1.15 mg/dL) experienced moderate diarrhea (non-serious) after initial placement of the ITCA 650 20 mcg/day study device from Study Day 8 through Study Day 13. On Study Day 87, the initial ITCA 650 60 mcg/day study device was placed; eGFR was 78 ml/min, creatinine 0.95 mg/dl and BUN 23 mg/dL. On Study Day 90, the patient was started on bumetanide for his hypertension. From Study Day 105 to 108, the patient's hypertension worsened (moderate, non-serious), and he developed nephrolithiasis (SAE, moderate); the kidney stones passed spontaneously. On Study Day 117, the patient developed severe diarrhea (SAE), severe dehydration (non-serious) and moderate acute renal failure (SAE) which required hospitalization. Per the hospital admission note, the patient had been experiencing diarrhea 3-4 times/day and nocturnal diarrhea since study device placed. Labs revealed an increased BUN of 39 mg/dL, increased creatinine of 2.3 mg/dL, and decreased eGFR of 28 ml/min. *Clostridium difficile* testing was negative, renal ultrasound was unremarkable, and colonoscopy noted extensive diverticulosis without evidence of diverticulitis or inflammatory bowel disease. The patient was treated with IV fluids and diphenoxylate/atropine. By Study Day 121, the dehydration, diarrhea and acute renal failure were considered resolved and the patient was discharged. The ITCA 650 device was removed on Study Day 127 due to diarrhea, and at that time, eGFR was 73 ml/min, creatinine 1.0 mg/dL, and BUN 19 mg/dL. **Intarcia assessment:** Relationship of ITCA 650 to diarrhea leading to volume depletion and AKI is considered probable. Diuretics, with recent addition of bumetanide (a potent diuretic), along with chronic use of an ACE inhibitor are probable contributing factors to the development of AKI.								

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Sponsor Assessment of Causality	Disposition
107-005	Day 111	60 mcg	CVA, CAD, Hypertension	Moderate impairment (3a)	Volume depletion due to mild vomiting	ARB	Yes; mild vomiting + con meds	Probable	Recovered on Tx / Completed Tx
SUMMARY	**Preferred Term: Renal Failure (Verbatim: Renal Failure)** – 43-year-old Caucasian male with baseline eGFR 48 mL/min; creatinine 1.60 mg/dL; BUN 24 mg/dL) experienced vomiting (non-serious, mild) from Study Day 4 to 18 after initial placement of 20 mcg/day device. On Study Day 94, the ITCA 650 60 mcg/day device was placed and labs showed creatinine 1.34 mg/dL, BUN 18 mg/dL and eGFR 58 mL/min. This same day the patient was started on losartan and rosuvastatin and developed vomiting (non-serious, mild), which was treated with ondansetron starting on Study Day 107. On Study Day 111, the patient presented to the hospital with myalgias and continued vomiting, and was admitted for dehydration (non-serious, moderate) and renal failure (SAE, moderate). On admission, creatinine was 2.6 mg/dL, and an abdominal ultrasound demonstrated gallstones and “intense bloating”. The patient was diagnosed with gallstones on Study Day 112. The site confirmed ultrasound report and additional labs (including CK values) were not available and treatment in hospital was unknown. On Study Day 113, creatinine decreased to 1.40 mg/dL, the patient was discharged, and the AKI was considered resolved. On Study Day 120, treatment for vomiting was changed from ondansetron to promethazine and the vomiting resolved on Study Day 130. On Study Day 129, the patient was noted to have increased creatinine (non-serious, mild) with creatinine 1.65 mg/dL, BUN 24 mg/dL and eGFR 46 mL/min. Increased creatinine remained ongoing at the end of the study. **Intarcia assessment:** Renal failure secondary to volume depletion from mild vomiting; relationship to ITCA 650 treatment is considered probable. A recently started ARB is a potential contributing factor to the development of AKI.								

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Sponsor Assessment of Causality	Disposition
107-007	Day 75	20 mcg	Hypertension, MI, Coronary Stent, Hyperparathyroidism, UTIs, Ex-Smoker	Moderate impairment (3a)	Volume loss due to Nausea, Vomiting, Diarrhea	Diuretics, Hypercalcemia, Hyponatremia, ACE-I, UTI	Yes; Moderate GI AEs + con meds	Possible	Recovering at time of Tx Discontinuation
SUMMARY	**Preferred Term: Acute kidney injury (Verbatim: Renal failure acute)** – 68-year-old Caucasian female (baseline eGFR 57 ml/min; BUN 21 mg/dL; creatinine 0.97 mg/dL) developed nausea and vomiting (both non-serious, moderate) on Study Day 67, and diarrhea (non-serious, moderate) on Study Day 70. On Study Day 75, the patient presented to the ER with nausea, vomiting, diarrhea, upper abdominal pain, poor oral intake, weakness and two syncopal episodes; and was admitted with diagnoses of dehydration (SAE, moderate), UTI (SAE, severe) and AKI (SAE, severe). Orthostatic hypotension was noted. Laboratory tests revealed BUN of 36 mg/dL, creatinine of 1.8 mg/dL, eGFR of 28 mL/min, WBC 10.9 k/uL and lactic acid 2.3 uMol/L. Urine culture was positive for Klebsiella, and a presumptive diagnosis of urosepsis was made; blood and stool cultures were negative. Treatment included IV fluids, ondansetron, ceftriaxone; lisinopril was discontinued. On Study Day 76, the hypotension had responded well to fluids; nausea, vomiting, diarrhea, dehydration and UTI were resolved and the patient was discharged. At discharge, creatinine was 1.3 mg/dL, BUN 27 mg/dL, eGFR 41 mL/min, WBC 6.3 k/uL, and blood cultures remained negative. On study day 92, the patient underwent scheduled replacement of ITCA 650 with the 60 mcg/day device; creatinine was 1.56 mg/dL, BUN 22 mg/dL and eGFR was 33 mL/min. No nausea, vomiting or diarrhea were reported after dose escalation. On Study Day 155, labs showed creatinine 1.85 mg/dL, BUN 48 mg/dL, eGFR of 27 mL/min and calcium 11.0 mg/dL.On Study Day 163, a nephrology consultation was obtained to evaluate worsening renal function with an unclear cause and considered unlikely to be related to study drug and recurrent hypercalcemia likely due to existing hyperparathyroidism. At that time creatinine was 1.5 mg/dL, BUN 30 mg/dL and eGFR 37 mL/min and the patient was noted to have Stage III chronic kidney disease (non-serious, moderate). On Study Day 171, labs showed creatinine 1.89 mg/dL, BUN 24 mg/dL and eGFR 26 mL/min. On Study Day 172, the patient had moderate nausea and vomiting which resolved the next day. On study day 173, the patient experienced a UTI and dehydration and was noted to have hyponatremia and hypokalemia. Treatment included ceftriaxone, potassium chloride and normal saline bolus. On Study Day 174, renal ultrasound showed normal kidneys. On Study Day 175, during a nephrology follow-up it was noted the patient had inadvertently continued her hydrochlorothiazide which was felt to be the cause of the hypokalemia. The hydrochlorothiazide was discontinued, and the patient was given additional potassium chloride and IV fluids. The hyponatremia was felt due to volume depletion which could have contributed to the renal dysfunction. On Study Day 183, during a scheduled visit, the ITCA 650 device was removed due to previous episode of AKI; labs at the time showed creatinine 1.54 mg/dL, BUN 18 mg/dL and eGFR 33 mL/min. On Study Day 195, hyponatremia and hypokalemia resolved and creatinine was 1.0 mg/dL. On Study Day 198, the AKI was considered resolved with sequelae of chronic kidney disease. On Study Day 225, at the end of study visit, creatinine was 0.87 mg/dL, BUN 23 mg/dL and eGFR 65 mL/min and the Stage III chronic kidney disease was considered resolved on Study Day 233. **Intarcia assessment:** Complex case with multiple potential confounding factors. Relationship between ITCA 650 and GI events with subsequent volume depletion and initial AKI identification is considered possible. Thereafter, this patient experienced waxing and waning deterioration of renal status with an overlay of both chronic and subacute precipitating factors. HCTZ treatment also a contributing factor to volume depletion (and hyponatremia, hypokalemia, hypercalcemia).								

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Sponsor Assessment of Causality	Disposition
107-008	Day 559	60 mcg	Hypertension, Cholelithiasis, RA, Former Smoker	Mild impairment	Volume depletion due to intermittent nausea, vomiting and diarrhea	Bilious Vomiting, Diarrhea, Idiopathic Nephrolithiasis	Yes; (however, GI AEs very late on day 559, and none prior not consistent)	Possible	Recovered on Tx / Completed Tx
SUMMARY	**Preferred Term: Acute Kidney Injury (Verbatim: Acute Renal Failure)** – 64-year-old Caucasian female with baseline eGFR 83 ml/min; BUN 10 mg/dL and creatinine 0.71 mg/d. On Study Day 458, BUN and creatinine were 12 mg/dL and 0.7 mg/dL respectively. On approximately Study Day 544 (86 days following placement of the third consecutive 60 mcg device), the patient started experiencing intermittent nausea and vomiting and around Study Day 557 she developed diarrhea and acute gastroenteritis (non-serious, moderate). On Study Day 559, the patient presented to the ER due to continued nausea, vomiting, diarrhea and a syncopal episode that morning; she was admitted due to acute renal failure (SAE, severe). On admission, creatinine was 8.45 mg/dL, BUN 51 mg/dL and eGFR 5 mL/min. Abdominal ultrasound revealed nephrolithiasis, normal pancreas and the right kidney had an echo dense mass of 8 mm. IV hydration was started. On Study Day 560, the patient became anuric; BUN was 59 mg/dL, creatinine was 9.26 mg/dL, eGFR was 4 mL/min, and urinalysis showed WBC 500 Leu/µL, RBC 27/hpf, bilirubin 3 mg/dL, positive nitrite, protein 3 g/L, and positive bacteria. The patient was started on ceftriaxone and enoxaparin, IV fluids was continued, and tube feeding started. On Study Day 561, hemodialysis was initiated, and the patient had 2 sessions during hospitalization. The cause of the GI symptoms and resulting volume depletion was thought to be acute gastroenteritis; an upper GI endoscopy (done on Study Day 569) noted gastritis as well as esophagitis. By Study Day 568, labs showed creatinine 0.62 mg/dL, BUN 5 mg/dL and eGFR >90 mL/min. By hospital discharge, the patient's nausea, vomiting and diarrhea had stopped. On Study Day 570 (day of hospital discharge), the non-serious event of acute gastroenteritis and the SAE of acute kidney injury were considered resolved. Additional laboratory tests over 100 days after this event included creatinine 0.7 mg/dL, BUN 12 mg/dL, and eGFR 84 mL/min. **Intarcia assessment:** AKI secondary to dehydration from intermittent vomiting, diarrhea and nausea with endoscopically confirmed esophagitis and gastritis. Relationship to ITCA 650 treatment is considered possible; however, the late onset date is unusual in the absence of any preceding GI symptoms earlier in the course of therapy and the endoscopic finding of gastritis and esophagitis may represent alterative diagnoses.								

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Sponsor Assessment of Causality	Disposition
107-013	Day 1 (randomization) **prior to first ITCA placement**	20 mcg	Nephropathy, Angina, Ischemic Stroke	Moderate impairment (3a)	Underlying Renal Disease identified by Day 1 Labs prior to ITCA Placement. No GI symptoms reported.	ARB, Diuretics, NSAID, Chronic Pyelonephritis, Marked Hyperglycemia	No; No GI Symptoms involved at any time around the event	Unlikely	Recovered on Tx / Completed Tx

SUMMARY

Preferred Term: Renal Impairment (Verbatim: Worsening of Renal Function) – 63-year-old Caucasian male with screening eGFR 63 mL/min, creatinine 1.17 mg/dL, and BUN 30 mg/dL 21 days prior to randomization. On Study Day 1 (randomization) baseline laboratory tests were obtained at 8:20 AM, prior to ITCA 650 placement that occurred at 9:05 AM. When these test results returned, the investigator noted moderate worsening of renal function with baseline pre-treatment labs showing eGFR 52 mL/min, creatinine 1.38 mg/dL and BUN 44 mg/dL. On Study Day 5, the patient was informed of his renal lab results and advised to consult with a nephrologist; no GI symptoms were noted. On Study Day 8, the patient was hospitalized by the nephrologist for further diagnostic evaluation of renal impairment. Labs on admission showed creatinine of 1.8 mg/dL, BUN 40 mg/dL, glucose 264.6 mg/dL, and Hgb 13.6 g/L. The patient reported no symptoms of nausea, vomiting, or diarrhea. An abdominal ultrasound showed diffuse pathology of renal parenchyma, chronic pyelonephritis, and prostate hypertrophy. Gastrointestinal studies showed erosive gastritis, chronic colitis and colonic diverticulum. Torasemide and furosemide were held, and spironolactone was discontinued. Treatment included pantoprazole, rebamipide, corvitine, Actovegin, Thiogamma, Strophantin K, inosine, and Renalgan. On Study Day 16, renal impairment was considered resolved and the patient was discharged with creatinine of 1.5 mg/dL and BUN of 24 mg/dL.

Overall progression of serum creatinine and BUN are provided in the table below:

	Day -21	Day 0	Day 8	Day 16
BUN (mg/dL)	30	44	40	24
Creatinine (mg/dL)	1.17	1.38	1.8	1.5

Intarcia assessment: Onset of worsening renal impairment noted on Day 1 (randomization) prior to ITCA 650 placement, with evidence of elevated BUN and creatinine in addition to declining eGFR from screening to baseline. Subject had underlying mild/moderate nephropathy, chronic pyelonephritis, renal cysts, marked hyperglycemia and treatment with multiple diuretics and an ARB, all of which provide a plausible explanation for the event. No GI events were reported. Relationship to ITCA 650 unlikely. The previous determination of this renal event as being treatment-emergent was revised in light of specific timing of lab testing and ITCA 650 placement and was reclassified as a Non-Treatment-Emergent AE.

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Sponsor Assessment of Causality	Disposition
107-009	Day 500	60 mcg	Angina, CHF, Hypertension, Smoker	Moderate impairment (3a)	Hemorrhage, no GI AEs	ARB	No; No GI AEs	Unlikely	Recovered on Tx / Completed Tx
SUMMARY	**Preferred Term: Acute Kidney Injury (Verbatim: Acute kidney injury)** – 66-year-old Caucasian female (baseline eGFR 58 ml/min; BUN 22 mg/dL; creatinine 0.97 mg/dL; BP 125/62 mmHg) developed non-serious events of increased creatinine (1.45 mg/dL) and decreased eGFR (36 mL/min) on Study Day 456. On this same day, blood pressure was 128/69 mmHg and heart rate was 72 bpm. On Study Day 501, the patient underwent bilateral lower extremity cauterization for venous incompetence. On Study Day 502, the patient was sent to the ER by a home health MD due to uncontrolled bleeding from the site of the vascular procedure in her right lower extremity. On arrival at the ER she was hypotensive (92/44 mmHg) and was transferred to another hospital for a higher level of care. On admission she had a supratherapeutic INR (serious, severe) and acute kidney injury (SAE, severe); she had been on Coumadin due to history of DVT and had not checked her INR for over one month. Significant labs on admission were BUN 53 mg/dL, creatinine 2.6 mg/dL, hemoglobin 9.8 g/dL and INR >10. Treatment included IV fluids, fresh frozen plasma, vitamin K, and transfusion of packed red blood cells. Metformin, Coumadin and blood pressure medications were held. The cause of the acute kidney injury was reported as blood loss and volume depletion. On Study Day 503, labs were creatinine 1.3 mg/dL, BUN 33 mg/dL, eGFR 44 mL/min, hemoglobin 10.6 g/dL and INR 2.8. The patient's blood cultures from the outlying ER returned positive for Gram-positive cocci (confirmed as staphylococcus); she remained hypotensive (85/55 mmHg) but was afebrile with normal WBC. She was started on vancomycin and given additional IV fluids. On Study Day 506, the patient had no further bleeding, repeat blood cultures from the admitting hospital returned negative, blood pressure was at baseline and renal function had normalized. She was discharged that day with creatinine 0.8 mg/dL, BUN 18 mg/dL, eGFR >60 mL/min, hemoglobin 10.3 and INR 1.3. Metformin, antihypertensives and Coumadin were restarted. On Study Day 541, the AEs of increased creatinine and decreased eGFR were considered resolved. On Study Day 772, creatinine was 1.03 mg/dL, BUN 21 mg/dL and eGFR 53 mL/min. No GI adverse events were reported at any time during the study. **Intarcia assessment:** AKI resulting from acute hypovolemia secondary to blood loss following a vascular procedure. No GI AEs. Relationship to ITCA 650 unlikely.								

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Sponsor Assessment of Causality	Disposition
107-010	Day 748	60 mcg	CAD, Hypertension, TIA, Carotid Stent, CKD	Moderate impairment (3a)	Volume loss due to Nausea, Vomiting, and Dehydration	NSAID, Antibiotic use, Gastritis, Odontogenic Infection	Yes, on some; note GI AEs very late onset; also, con meds + other conditions	Unlikely	Recovered prior to Tx Discontinuation
SUMMARY	**Preferred Terms: Acute Kidney Injury (Verbatim: Acute Kidney Injury, due to Dehydration** – 73-year-old Caucasian male (baseline eGFR 50 ml/min; BUN 29 mg/dL; creatinine 1.39 mg/dL) was noted by the PI to have developed moderate nausea and vomiting (both non-serious) from Study Day 609 to 747. On Study Day 747, the patient was started on amoxicillin and pain medications for a dental abscess. On Study Day 748, the patient presented to his PCP with complaints of increasing nausea and vomiting since early morning, with one syncopal episode. He denied abdominal pain and diarrhea. It was noted that the patient had been taking his antibiotics and pain medications on an empty stomach. The patient was sent to the hospital and admitted for the first time due to dehydration (SAE, severe), nausea (upgraded to serious and severe), vomiting (upgraded to serious and severe), ketonuria (SAE, moderate), and AKI (SAE, severe). Labs showed creatinine 1.7 mg/dL (vs baseline of 1.39), BUN 25 mg/dL (baseline 29), glucose 150 mg/dL, sodium 135 mmol/L, anion gap 10, and negative acetone. The patient had documented orthostatic hypotension and was treated with IV fluid boluses and ondansetron. On Study Day 749, creatinine was 1.4 mg/dL with BUN 20 mg/dL. The patient was discharged to home, and the serious AKI event was considered resolved. At that time the PI reported Stage 3 chronic kidney disease as a non-serious AE. On Study Day 751, the patient returned to the ER and was subsequently readmitted to the hospital due to increased weakness, confusion, fever (up to 101.6) and decreased oral intake. Relevant labs revealed sodium 124 mmol/L, glucose 125 mg/dL, anion gap 14, creatinine 1.3 mg/dL, BUN 19 mg/dL, and eGFR 58 ml/min; hemoglobin and liver function tests were within normal limits. Treatment included IV fluids, 3% normal saline for hyponatremia, empiric antibiotics for suspected bacterial gastroenteritis, and a protein pump inhibitor. A GI consult was obtained and noted that the patient had been taking NSAIDs, usually several times per week. Upper GI endoscopy confirmed mild erythematous gastritis and duodenitis but was otherwise normal. From Study Day 752 to 755, creatinine ranged from 1.0 to 1.10 mg/dL, BUN 12-16 mg/dL and eGFR remained >60mL/min. On Study Day 756, the patient was discharged with a creatinine of 1.1 mg/dL, BUN 14 mg/dL, eGFR >60 ml/min and sodium 130 mmol/L. On Study Day 758, the ITCA 650 study device was removed; creatinine was 1.55 mg/dL, BUN 25 mg/dL and eGFR 44 ml/min at that time. The nausea and vomiting, which had continued intermittently since Study Day 748, were considered resolved by the PI on Study Day 784 while the Stage 3 chronic kidney disease remained ongoing at end of study. **Intarcia assessment:** Case was KDIGO grade 0. Complex case with acute kidney injury superimposed on chronic kidney disease. Laboratory documentation for AKI was not available during either hospitalization, with available creatinine values overall similar to baseline values. Symptoms are consistent with volume depletion; onset of nausea and vomiting very late in the course of therapy around time of diagnosis of a dental abscess and exacerbated by administration of amoxicillin and pain medications that were reportedly taken on an empty stomach. Relationship to ITCA 650 administration is considered unlikely.								

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Sponsor Assessment of Causality	Disposition
107-011	Day 281	60 mcg	MI, Cardiac Stent, Former Smoker	Mild impairment	Volume depletion due to mild Diarrhea and Vomiting with Concurrent NSAID use	Multiple NSAIDs and ARB, + Antibiotics and UTI	No; mild GI AEs late in therapy with no prior GI AEs; note con meds + other conditions	Unlikely	Recovered on Tx / Completed Tx
SUMMARY	**Preferred Term: Acute Kidney Injury (Verbatim: Acute Kidney Injury)** – 75-year-old Caucasian female with baseline eGFR 64 mL/min, creatinine 0.87 mg/dL and BUN 15 mg/dL. On Study Day 266 the second ITCA 650 60 mcg/day device was placed, and on that same day she was diagnosed with a urinary tract infection (non-serious, mild); acute kidney injury (SAE, moderate) was also reported, but labs showed creatinine 0.88 mg/dL, BUN 14 mg/dL and eGFR 63 mL/min, which did not support the PIs report of AKI onset on that date. Up to this point the patient had no GI symptoms around previous ITCA 650 device placements. On Study Day 271, per the PI, the patient developed vomiting (non-serious, mild) and diarrhea (non-serious, mild). On Study Day 272, the patient was started on ciprofloxacin for the UTI which was given for 3 days and stopped on Study Day 274. On Study Day 281, the patient was admitted to the hospital for AKI after labs performed during an outpatient follow-up visit revealed an increased BUN and creatinine of 43 mg/dL and 3.0 mg/dL respectively, and a decreased eGFR of 16 mL/min.; repeat labs following admission showed creatinine 2.8 mg/dL and BUN 41 mg/dL. Treatment included intravenous fluids and temporary suspension of metformin, olmesartan and NSAIDs. Per nephrology consult during hospitalization, the patient developed some diarrhea prior to beginning the ciprofloxacin, then after starting the antibiotic she became weak and fatigued with decreased appetite, some nausea and vomiting, and continued episodes of diarrhea. She also reported abdominal bloating and occasional abdominal pain. The patient admitted to routinely taking multiple NSAIDS for low back pain prior to taking the ciprofloxacin and being hospitalized. The nephrologist concluded that the AKI was likely secondary to prerenal azotemia from nausea, vomiting, diarrhea, decreased oral intake and NSAID use, with possible contribution of recent antibiotic use; GI symptoms could have also been related to viral gastroenteritis. On Study Day 282, creatinine was down to 2.4 and BUN 35. On Study Day 284, creatinine was noted to be in normal range; the patient was discharged, and AKI was considered resolved. On Study Day 290, renal function had returned to baseline with creatinine 1.1 mg/dL. **Intarcia assessment:** Acute renal insufficiency due to hypovolemia from mild diarrhea and vomiting (exact timing unclear per records) secondary to questionable viral gastroenteritis vs antibiotic use, with concurrent use of multiple NSAIDs and olmesartan potentially contributing to renal impairment. Relationship to ITCA 650 considered unlikely.								

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Sponsor Assessment of Causality	Disposition
107-012	Day 312 (44 days post Tx Discontinuation)	60 mcg	Hypertension, MI, CABG, Ex-Smoker, Sleep Apnea	Mild impairment	Severe volume depletion most likely secondary to diuretics. No GI AEs reported	ACE-I, Diuretics	No	Unlikely	Discontinued Tx 44 days prior to Event
SUMMARY	**Preferred Term: Acute Kidney Injury (Verbatim: Acute Kidney Failure)** – 65-year-old Caucasian male (baseline eGFR 80 ml/min; BUN 13 mg/dL; creatinine 0.95 mg/dL) was hospitalized with dehydration and AKI (SAEs, severe) on Study Day 312, 44 days after the last ITCA 650 device was removed. At the time of last device removal at the EOT visit on Study Day 268 (patient did not complete study per protocol due to site closure), labs showed creatinine 1.2 mg/dL, BUN 28 mg/dL and eGFR 61 mL/min. There were no reported signs or symptoms that led up to the events of dehydration and AKI, and no relevant laboratory or diagnostic tests were provided as hospital records were not obtained (patient lost to follow-up). Treatment included rehydration with IV saline. The patient was discharged on Study Day 314 with resolution of dehydration and AKI. No adjustments to diabetic medications were noted following ITCA 650 removal and there were no reported AEs of nausea or vomiting during study participation. Last know labs were on Study Day 462 with creatinine 1.41 mg/dL, BUN 29 mg/dL and eGFR 50 mL/min. **Intarcia assessment:** Dehydration and subsequent AKI 44 days after ITCA 650 treatment discontinued. Etiology of volume depletion unclear, possibly related to diuretic use with chronic use of ACE-I increasing risk of renal injury. Relationship to ITCA 650 unlikely and this case is not considered treatment-emergent since it occurred approximately 6 weeks post device removal.								

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Disposition
107-014	Day 460	Placebo	Ex-smoker	Mild impairment	Volume contraction due to hyperosmolar hyperglycemic state, Septic shock of urinary origin	Vomiting, UTI, Antibiotic use	No; although GI AEs (vomiting) and severe dehydration + con meds + other conditions	Not Recovered /Not Resolved prior to Death
SUMMARY	**Preferred Term: Acute kidney injury (Verbatim: Acute renal failure)** – 67-year-old Caucasian male (baseline eGFR 87 mL/min; BUN 23 mg/dL; creatinine 0.88 mg/dL) presented with fever, vomiting, and abdominal pain and was diagnosed with a non-serious AE of urinary tract infection (severe) on Study Day 453. Treatment included trimethoprim/sulfamethoxazole and acetaminophen as needed. On Study Day 457, the patient returned to the site for an unscheduled site visit where labs revealed glucose 621 mg/dL, HbA1c 15.0%, BUN 37 mg/dL, creatinine 1.61 mg/dL and eGFR 43 mL/min and treatment with amikacin (IM) and ciprofloxacin (PO) was initiated. On Study Day 460, the patient presented with disorientation and hallucinations and was hospitalized with a diagnosis of hyperosmolar hyperglycemic state (SAE, moderate), septic shock (urosepsis - SAE, severe) and acute kidney injury (SAE, severe); with severe dehydration, metabolic acidosis, and upper GI bleeding. Blood pressure on admission was 50/30 mmHg with heart rate 112 bpm. Labs revealed glucose 900 mg/dL, BUN 122 mg/dL, and creatinine 2.5 mg/dL. Hydronephrosis was noted on an imaging study. Treatment included fluid resuscitation, transfusion of packed red blood cells, intubation with airway management, vasopressors, antibiotics, and steroids. On Study Day 461, creatinine ranged from 2.0 to 1.7 mg/dL and BUN 228 to 196 mg/dL; in addition, blood pressure ranged from 80/50 to 60/30 mmHg with heart rate 78-105 bpm. Systemic inflammatory response syndrome was suspected secondary to urosepsis. On Study Day 462, bradycardia progressed to asystole and resuscitation was unsuccessful, with septic shock and diabetes mellitus noted as causes of death. **Intarcia assessment:** Hyperosmolar hyperglycemic state and urosepsis with septic shock with volume depletion, vomiting, severe dehydration, and hypotension leading to acute kidney injury and subsequent cardiovascular collapse and death.							

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Disposition
107-015	Day 632	Placebo	Hypertension, Ischemic cardiomyopathy, and peripheral artery disease	Mild impairment	Volume contraction and dehydration due to several days of diarrhea. Use of ACE-I	ACE-I, acetylsalicylic acid	Yes; GI AEs + con meds	Recovered on Tx / Completed Tx
SUMMARY	**Preferred Term: Renal failure (Verbatim: Renal failure)** – 62-year-old Hispanic female with baseline eGFR 80 mL/min, BUN 20 mg/dL and creatinine 0.74 mg/dL. Laboratory results at a scheduled study visit on Study Day 452 revealed elevated BUN at 25 mg/dL, creatinine at 1.00 mg/dL and decreased eGFR at 56 mL/min. From Study Days 619 to 627, the patient experienced moderate diarrhea (non-serious). On Study Day 632, laboratory tests at a scheduled study visit revealed BUN at 72 mg/dL, creatinine at 1.92 mg/dL, and eGFR at 26 mL/min. The patient was diagnosed with renal failure (SAE, severe, medically significant but not hospitalized) by the PI. Treatment for the event included suspension of metformin and oral hydration. On Study Day 640, study labs showed creatinine 1.04 mg/dL, BUN 25 mg/dL and eGFR 54 mL/min. and the event of renal failure was considered resolved. The patient completed the study per protocol. **Intarcia assessment:** Volume contraction in the setting of diarrhea leading to dehydration provide a plausible explanation for the pre-renal AKI. ACE-I treatment could also be a contributing factor.							

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Disposition
107-016	Day 168	Placebo	Nephropathy, Hypertension, MI, CHF, Non-alcoholic fatty liver disease, ex-smoker	Moderate impairment (3a)	Possible contrast induced nephropathy	Contrast dye from coronary angiography, use of acetylsalicylic acid, and ARB	No	Recovered on Tx / Resolved prior to Death
SUMMARY	**Preferred Term: Acute kidney injury (Verbatim: Acute renal failure)** – 71-year-old Caucasian male with history of nephropathy and baseline eGFR 55 mL/min, BUN 27 mg/dL, and creatinine 1.29 mg/dL. Follow-up labs on Study Day 91 showed creatinine 1.17 mg/dL, BUN 21 mg/dL and eGFR 21 mL/min. On Study Day 162 the patient was hospitalized for coronary angiography for worsening myocardial ischemia and was discharged on Study Day 167. On Study Day 168, the patient developed anuria and was diagnosed with acute renal failure (SAE, severe); lab results from this day not provided. On Study Day 170, labs revealed creatinine of 7.92 and 7.35 mg/dL. On Study Day 171, the patient was admitted to the ICU due to elevated creatinine and AKI, which was felt to be secondary to the contrast dye administered for the coronary angiogram. By Study Day 181, the patient's creatinine had decreased to 0.92 mg/dL, the AKI was considered resolved, and the patient was discharged. On Study Day 213, the patient died at home due to unknown causes. Per the family, the patient had no new complaints prior to death; no additional information was available. **Intarcia assessment:** Patient with history of nephropathy developed acute renal failure secondary to radiocontrast dye administered for coronary angiography.							

Patient	Study Onset Day (Renal Diagnosis)	Dose at time of AKI Event Onset	Selected Medical Hx	Baseline Renal Function	Primary Etiology	Contributing Factors	Fits Pattern for AKI as shown in GLP-1 RA class labeling	Disposition
107-017	Day 107	Placebo	Hypertension, Nephropathy	Mild impairment	Hypotension and volume contraction due to diarrhea, vomiting and decreased PO intake	Amoxycillin – clavulanate, ARB, diuretics, blood loss	Yes	Recovered prior to Tx Discontinuation
SUMMARY	**Preferred Term: Acute kidney injury (Verbatim: Renal failure acute)** – 70-year-old Caucasian female with baseline eGFR 65 mL/min, BUN 24 mg/dl, and creatinine 0.86 mg/dl. Laboratory results at a scheduled visit on Study Day 92 showed a creatinine at 0.96 mg/dL, BUN 30 mg/dL, and eGFR was 57 mL/min. On Study Day 102, the patient was started on amoxicillin/clavulanic acid after having an inguinal furuncle drained (non-serious, moderate). On Study Day 107, the patient presented to the ER with a 3 day history of diarrhea and vomiting and one day of decreased urine output; during this time she continued to take her ARB, diuretics and metformin. Labs in the ER showed creatinine 8.66 mg/dL, BUN 211 mg/dL and potassium 7.1 mEq/L; the patient was hospitalized for acute kidney injury (SAE, severe). An ultrasound demonstrated normal kidneys. Treatment included intravenous saline, Kayexalate, insulin, sodium bicarbonate, and short-term dialysis. The patient was also noted to be anemic, possibly due to bleeding from the groin wound. On Study Day 108, wound culture was positive for *S. aureus,* which was treated with a 7-day course of ceftriaxone. On Study Day 113, creatinine was down to 2.56 mg/dL and BUN was 110 mg/dL; dialysis was discontinued. AKI was considered resolved and the patient was discharged on Study Day 114 with creatinine of 1.81 mg/dL and BUN 95 mg/dL. A follow-up creatinine on Study Day 120 was 0.91 mg/dL. There was no action taken with study drug. The patient did not complete the study per protocol due to having initiated therapy with an excluded medication and the device was removed on study day 141. **Intarcia assessment:** Acute kidney injury due to pre-renal azotemia and hypotension from vomiting and diarrhea associated with the use of antibiotics while continuing diuretics. The patient also had acute blood loss from the inguinal wound, the significance of which is unknown.							

13.2 Study 107 Study Enrollment, Disposition and Baseline Characteristics

13.2.1 Study 107 Enrollment Criteria

Key inclusion criteria included:

- Adult male and female patients with a diagnosis of T2DM (≥ 3 months prior to screening) and a baseline HbA_{1c} of ≥ 6.5% who met the following criteria
  - High Risk: ≥ 40 years of age with a history of at least 1 documented occurrence of CAD, cerebrovascular disease, or symptomatic PAD and whose disease, in the Investigator's opinion, was stable; or
  - Low Risk: ≥ 60 years of age with at least 1 other CV risk factor in addition to T2DM.
- Patients on a stable regimens of diet and exercise alone or in combination with insulin (intermediate and/or long-acting) or other oral mono- or combination anti-diabetic therapies with the exception of DDP-4 inhibitors, SGLT2 inhibitors, and incretin mimetics.

Key exclusion criteria included:

- Treatment with the following anti-diabetic agents within 3 months prior to screening: DPP-4 inhibitor, GLP-1 agonist, or SGLT2 inhibitors
- History or evidence of any of the following: Type 1 diabetes or secondary forms of diabetes, metabolic complications, thyroid cancer, acute or chronic pancreatitis, weight loss surgery, chronic infectious liver disease
- FPG > 270 mg/dL (15 mmol/L) at screening
- Uncontrolled hypertension
- NYHA Grade III or IV congestive heart failure
- eGFR < 50 mL/min/1.73 m^2 at screening

13.2.2 Study 107 Statistical Methods

All randomized patients were included in the ITT population, which included all randomized patients regardless of drug exposure. The first mITT (mITT-1) population included all randomized patients who had a procedure started for the initial ITCA 650/ITCA placebo placement. The second mITT population (mITT-2) included all patients in the mITT-1 population who had a valid baseline and at least 1 post-baseline HbA_{1c} result. An EE population comprised all patients in the mITT-2 population who did not prematurely discontinue treatment or who did not have a major protocol deviation. Exploratory efficacy, pharmacodynamics, and metabolic laboratory endpoints were analyzed using the mITT-2 and EE populations.

Comparisons of treatment groups for each change from baseline in exploratory pharmacodynamic and metabolic laboratory parameters were based on an MMRM model. Change from baseline was the dependent variable, while treatment, baseline result, CV risk factor, treatment-by-visit interaction were set as fixed effects unless otherwise specified. Results were presented by each on-treatment visit up to Month 27. Post-treatment follow-up periods were analyzed separately using MMRM. Month 33 on treatment, last on treatment, and last on study were analyzed using separate ANCOVA with change from baseline as the dependent variable, and with treatment, baseline results, and CV risk as factors. The end of treatment visits were mapped to the next scheduled visit in the analyses; therefore, although the maximum actual treatment exposure for any patient was 32 months, data for Month 33 visits are presented in applicable tables.

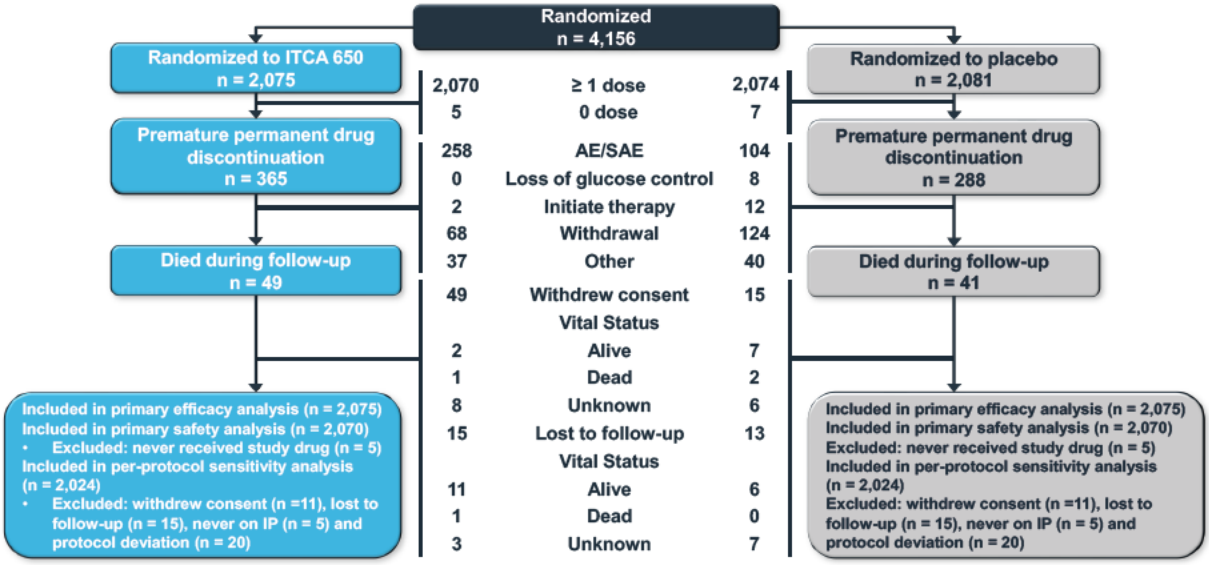
Comparison of the treatment groups for the < 7% and < 6.5% thresholds was based on a Cochran-Mantel-Haenszel test stratified by CV risk factor. The time to intensification of therapy and time to new insulin therapy were analyzed using Kaplan-Meier methods for each dose group. The median time to each of these events was estimated along with a 95% CI, if estimable.

Exploratory subgroup analyses were performed on the change from baseline HbA_{1c} and body weight.

13.2.3 Study 107 Patient Population

13.2.3.1 Disposition

Figure 42: Study 107 CVOT Consort Flow Diagram



13.2.3.2 *Demographics and Baseline Characteristics*

Table 41: Study 107 Demographics Overall (ITT Population)

Characteristic (unit)	ITCA 650 60 mcg/day (N = 2,075)	Placebo (N = 2,081)
Age (years)		
Mean (SD)	62.5 (7.98)	62.2 (8.26)
Median (Min, Max)	63.0 (40, 90)	63.0 (40, 87)
< 50 years (n [%])	124 (6.0%)	156 (7.5%)
50–64 years (n [%])	1,126 (54.3%)	1,106 (53.1%)
65–74 years (n [%])	695 (33.5%)	678 (32.6%)
≥ 75 years (n [%])	130 (6.3%)	141 (6.8%)
Sex, n (%)		
Male	1297 (62.5%)	1,334 (64.1%)
Female	778 (37.5%)	747 (35.9%)
Race, n (%)		
White	1909 (92.0%)	1913 (91.9%)
Black or African American	93 (4.5%)	93 (4.5%)
Asian	15 (0.7%)	22 (1.1%)
Asian Indian (Indian Subcontinent)	3 (0.1%)	7 (0.3%)
American Indian or Alaska Native	4 (0.2%)	5 (0.2%)
Native Hawaiian or Other Pacific Islander	1 (< 0.1%)	3 (0.1%)
Other	25 (1.2%)	14 (0.7%)
Multiple	25 (1.2%)	24 (1.2%)
Ethnicity, n (%)		
Hispanic or Latino	578 (27.9%)	583 (28.0%)
Not Hispanic or Latino	1,447 (69.7%)	1,442 (69.3%)
Not Reported	50 (2.4%)	56 (2.7%)
Region, n (%)		
North America	438 (21.1%)	439 (21.1%)
Early Eastern/Central Europe	178 (8.6%)	181 (8.7%)
Late Eastern/Central Europe	563 (27.1%)	566 (27.2%)
Western Europe	169 (8.1%)	170 (8.2%)
Asia Pacific and Middle East	225 (10.8%)	221 (10.6%)
Central and Latin America	502 (24.2%)	504 (24.2%)

ITT: intention-to-treat; n: number; N: total number

Note: Only the year of birth was collected. Age has been calculated as the year of enrollment minus the year of birth.

Table 42: Study 107 Baseline Characteristics Overall (ITT Population)

Characteristic (unit)	ITCA 650 60 mcg/day (N = 2,075)	Placebo (N = 2,081)
Weight (kg) (n)	2,073	2,081
Mean (SD)	93.94 (19.288)	93.55 (19.909)
Median (Min, Max)	92.00 (41.5, 197.5)	90.80 (39.0, 190.1)
Height (cm) (n)	2,066	2,078
Mean (SD)	168.2 (9.58)	168.7 (9.62)
Median (Min, Max)	168.2 (135, 198)	169.8 (120, 198)
BMI (kg/m^2) (n)	2,066	2,078
Mean (SD)	33.13 (6.027)	32.81 (6.063)
Median (Min, Max)	32.36 (15.3, 66.6)	31.93 (15.2, 59.4)
BMI Category (kg/m^2) (n)	2,075	2,081
< 30 (n [%])	682 (32.9%)	725 (34.8%)
30–< 35 (n [%])	691 (33.3%)	709 (34.1%)
≥ 35 (n [%])	693 (33.4%)	644 (30.9%)
Missing (n [%])	9 (0.4%)	3 (0.1%)
Smoking Status (n)	2,075	2,081
Current Smoker (n [%])	328 (15.8%)	323 (15.5%)
Past Smoker (n [%])	674 (32.5%)	694 (33.3%)
Never Smoked (n [%])	1,073 (51.7%)	1,063 (51.1%)
Missing (n [%])	0	1 (< 0.1%)
HbA_{1c} (%) (n)	2,074	2,081
Mean (SD)	8.37 (1.505)	8.35 (1.514)
Median (Min, Max)	8.00 (5.3, 14.5)	8.00 (5.2, 15.4)
≤ 8.5	1,277 (61.5%)	1,317 (63.3%)
> 8.5	797 (38.4%)	764 (36.7%)
Baseline HbA_{1c} (mmol/mol) (n)	2,074	2,081
Mean (SD)	67.99 (16.454)	67.76 (16.547)
Median (Min, Max)	63.90 (34.4, 135.0)	63.90 (33.3, 142.6)
Baseline Fasting Plasma Glucose (mmol/L) (n)	2,074	2,081
Mean (SD)	9.62 (3.132)	9.66 (3.172)
Median (Min, Max)	9.00 (3.1, 29.9)	9.00 (2.3, 29.0)
Baseline eGFR (ml/min/1.73 m^2) (n)	2,074	2,081
Mean (SD)	81.48 (19.039)	81.68 (18.923)
Median (Min, Max)	79.00 (20.0, 178.0)	80.00 (17.0, 186.0)
Baseline eGFR Category (ml/min/BSA) (n)	2,075	2,081
Normal (≥ 90) (n [%])	618 (29.8%)	625 (30.0%)

Characteristic (unit)	ITCA 650 60 mcg/day (N = 2,075)	Placebo (N = 2,081)
Mild (60–89) (n [%])	1,259 (60.7%)	1,242 (59.7%)
Moderate (30–59) (n [%])	196 (9.4%)	212 (10.2%)
Severe (15–29) (n [%])	1 (< 0.1%)	2 (0.1%)
Missing	1 (< 0.1%)	0
Baseline Systolic Blood Pressure (mmHg) (n)	2,075	2,081
Mean (SD)	137.42 (15.281)	137.67 (15.548)
Median (Min, Max)	137.50 (84.5, 185.0)	137.50 (84.5, 185.0)
Baseline Diastolic Blood Pressure (mmHg) (n)	2,075	2,081
Mean (SD)	78.95 (9.018)	79.19 (8.857)
Median (Min, Max)	79.50 (49.0, 110.5)	80.00 (43.5, 106.5)
Baseline Pulse (beats/min) (n)	2,075	2,081
Mean (SD)	72.68 (10.625)	73.18 (10.458)
Median (Min, Max)	72.00 (43.0, 116.0)	72.50 (44.0, 111.5)
Baseline Albumin/Creatinine Ratio	2,075	2,081
< 30 mg/g	1,359 (65.5%)	1,374 (66.0%)
≥ 30–≤ 300 mg/g	569 (27.4%)	570 (27.4%)
> 300 mg/g	144 (6.9%)	136 (6.5%)
Missing	3 (0.1%)	1 (< 0.1%)

BMI: body mass index; eGFR: estimated glomerular filtration rate; HbA_{1c}: glycosylated hemoglobin A_{1c}; ITT: intention-to-treat; n: number; N: total number; SD: standard deviation

Note: Baseline is defined as the last assessment on or before the day of the initial placement procedure of ITCA 650/placebo.

Note: Baseline blood pressure and heart rate results summarize the average of 2 measurements taken at the same visit.

Note: Treatment group comparisons are based on a Chi-square test for categorical variables and an ANOVA model with treatment group as a fixed effect for continuous variables.

Table 43: Study 107 Diabetes History Overall (ITT Population)

	ITCA 650 60 mcg/day (N = 2,075)	Placebo (N = 2,081)
Years Since Diabetes Diagnosis (n)	2,075	2,081
Mean (SD)	11.57 (7.598)	11.32 (7.460)
Median (Min, Max)	10.44 (0.3, 50.0)	10.20 (0.3, 65.3)
< 5 Years (n [%])	405 (19.5%)	429 (20.6%)
5–10 Years (n [%])	558 (26.9%)	578 (27.8%)
> 10 Years (n [%])	1,112 (53.6%)	1,074 (51.6%)
Stable Diabetes Treatment Regimen	2,074	2,081
Diet and Exercises Alone	46 (2.2%)	36 (1.7%)
Diet and Exercise in Combination With Medication	2028 (97.8%)	2045 (98.3%)
Patients with Comorbidity Risk Factors (n)	1,662 (80.1%)	1,630 (78.3%)
Nephropathy (n [%])	189 (9.1%)	204 (9.8%)
Neuropathy (n [%])	614 (29.6%)	583 (28.0%)
Retinopathy (n [%])	318 (15.3%)	303 (14.6%)
Nonalcoholic Fatty Liver Disease (n [%])	278 (13.4%)	237 (11.4%)
Obesity (n [%])	1,431 (69.0%)	1,388 (66.7%)
Discontinued Anti-diabetes Medications within 12 Months Prior to Screening (n)	2,075	2,081
Yes (n [%])	233 (11.2%)	198 (9.5%)
No (n [%])	1,842 (88.8%)	1,883 (90.5%)

CV: cardiovascular; ITT: intention-to-treat; n: number; N: total number
Note: Years since diabetes diagnosis = year of informed consent date - year of diagnosis.

Table 44: Study 107 Notable Medical History Terms (ITT Population)

	ITCA 650 n (%)	Placebo n (%)
All Patients	(N = 2,075)	(N = 2,081)
Obesity	1,431 (69.0%)	1,389 (66.7%)
Hypertension	1,753 (84.5%)	1,716 (82.5%)
Hyperlipidemia	420 (20.2%)	407 (19.6%)
Dyslipidemia	692 (33.3%)	714 (34.3%)
Hypercholesterolemia	246 (11.9%)	238 (11.4%)
High-risk CV Group	(N = 1,578)	(N = 1,581)
Obesity	1,096 (69.5%)	1,050 (66.4%)
Hypertension	1,342 (85.0%)	1,313 (83.0%)
Hyperlipidemia	291 (18.4%)	279 (17.6%)
Dyslipidemia	583 (36.9%)	593 (37.5%)
Hypercholesterolemia	166 (10.5%)	147 (9.3%)
Low-risk CV Group	(N = 497)	(N = 500)
Obesity	335 (67.4%)	339 (67.8%)
Hypertension	411 (82.7%)	403 (80.6%)
Hyperlipidemia	129 (26.0%)	128 (25.6%)
Dyslipidemia	109 (21.9%)	121 (24.2%)
Hypercholesterolemia	80 (16.1%)	91 (18.2%)

CV: cardiovascular; ITT: intention-to-treat; n: number; N: total number; SD: standard deviation

Table 45: Study 107 Notable Diabetes History Variations by CV Risk Group (ITT Population)

	ITCA 650 60 mcg/day	Placebo
Baseline CV Risk: High	N = 1,578	N = 1,581
Years Since Diabetes Diagnosis, n	1,578	1,581
Mean (SD)	11.10 (7.763)	10.79 (7.310)
Median (Min, Max)	9.46 (0.3, 50.0)	9.23 (0.3, 43.7)
Patients With Comorbidity Risk Factors	1,278 (81.0%)	1,234 (78.1%)
Nephropathy	163 (10.3%)	172 (10.9%)
Neuropathy	491 (31.1%)	464 (29.3%)
Retinopathy	272 (17.2%)	259 (16.4%)
Nonalcoholic Fatty Liver Disease	223 (14.1%)	188 (11.9%)
Obesity	1,096 (69.5%)	1,050 (66.4%)
Baseline CV Risk: Low	N = 497	N = 500
Years Since Diabetes Diagnosis, n	497	500
Mean (SD)	13.08 (6.843)	13.00 (7.681)
Median (Min, Max)	12.50 (0.6, 44.8)	12.06 (0.3, 65.3)
Patients With Comorbidity Risk Factors	384 (77.3%)	396 (79.2%)
Nephropathy	26 (5.2%)	32 (6.4%)
Neuropathy	123 (24.7%)	119 (23.8%)
Retinopathy	46 (9.3%)	44 (8.8%)
Nonalcoholic Fatty Liver Disease	55 (11.1%)	49 (9.8%)
Obesity	335 (67.4%)	338 (67.6%)

CV: cardiovascular; ITT: intention-to-treat; n: number; N: total number; SD: standard deviation

13.2.3.3 Concomitant Medications and Background Anti-Diabetic Medication

Table 46: Study 107 Background Anti-Diabetic Medication Taken at Baseline (ITT Population)

Category of Anti-Diabetic Medication	ITCA 650 60 mcg/day (N=2,075)	Placebo (N=2,081)
Number of Patients with Any Anti-Diabetic Medication Taken at Baseline (n [%])	2022 (97.4%)	2035 (97.8%)
Metformin Monotherapy (n%)	546 (26.3%)	544 (26.1%)
SU Monotherapy	81 (3.9%)	87 (4.2%)
TZD Monotherapy	1 (< 0.1%)	2 (0.1%)
Insulin, Fast-Acting	34 (1.6%)	33 (1.6%)
Insulin, Long-Acting	435 (21.0%)	425 (20.4%)
Insulin, Intermediate-Acting	237 (11.4%)	245 (11.8%)
Insulin, Combined	44 (2.1%)	43 (2.1%)
Insulin + Oral Anti-diabetes Medication	602 (29.0%)	595 (28.6%)
SU + TZD	3 (0.1%)	1 (< 0.1%)
SU + Metformin	621 (29.9%)	631 (30.3%)
TZD + Metformin	6 (0.3%)	10 (0.5%)
SU + TZD + Metformin	17 (0.8%)	18 (0.9%)

CV: cardiovascular; ITT: intention-to-treat; n: number; N: total number; SD: standard deviation; SU: sulfonylurea; TZD: thiazolidinedione

Note: Baseline is defined as the last assessment on or before the day of the initial placement procedure of ITCA 650/Placebo.

Note: The category of metformin monotherapy includes patients who took metformin as anti-diabetic medication without SU, insulin or TZD. The SU monotherapy and TZD monotherapy are similar.