**Food and Drug Administration**
**Center for Drug Evaluation and Research**

# Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting

**September 21, 2023**

Location: All meeting participants will be joining this advisory committee meeting via an online teleconferencing platform.

Topic: The Committee discussed the safety and efficacy of ITCA 650 (exenatide in DUROS device), a drug-device combination product that is the subject of a new drug application (NDA) submitted by Intarcia Therapeutics, Inc. (Intarcia) (NDA 209053), for the proposed indication, as an adjunct to diet and exercise, to improve glycemic control in adults with type 2 diabetes mellitus. CDER is holding this meeting pursuant to a March 24, 2023, letter from the Chief Scientist of FDA, Dr. Namandjé N. Bumpus, wherein she granted Intarcia's request under 21 CFR 12.32(b)(3)(ii) for a public hearing before an advisory committee in lieu of a formal evidentiary hearing. Intarcia requested a public hearing before an advisory committee on CDER's proposal to refuse approval of Intarcia's NDA for ITCA 650 (see Docket No. FDA-2021-N-0874).

These summary minutes for September 21, 2023 of the Endocrinologic and Metabolic Drugs Advisory Committee meeting of the Food and Drug Administration were approved on December 13, 2023.

I certify that I attended the September 21, 2023 meeting of the Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration and that these minutes accurately reflect what transpired.

/s/
LaToya Bonner, PharmD
Designated Federal Officer, EMDAC

/s/
Cecilia C. Low Wang, MD
Chairperson, EMDAC

# Final Summary Minutes of the Endocrinologic and Metabolic Drugs Advisory Committee Meeting

## September 21, 2023

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) of the Food and Drug Administration, Center for Drug Evaluation and Research, met on September 21, 2023. The meeting presentations were heard, viewed, captioned, and recorded through an online video conferencing platform. Prior to the meeting, the members and temporary voting members were provided the briefing materials from the FDA and Intarcia Therapeutics (an i2o Business Unit) (Intarcia). The meeting was called to order by Cecilia C. Low Wang, MD (Chairperson). The conflict of interest statement was read into the record by LaToya Bonner, PharmD (Designated Federal Officer). There were approximately 2091 people online. There was a total of 17 Open Public Hearing (OPH) speaker presentations.

A verbatim transcript will be available, in most instances, at approximately ten to twelve weeks following the meeting date.

**Agenda:**

The Committee discussed the safety and efficacy of ITCA 650 (exenatide in DUROS device), a drug-device combination product that is the subject of a new drug application (NDA) submitted by Intarcia (NDA 209053), for the proposed indication as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. CDER held this meeting pursuant to a March 24, 2023, letter from the Chief Scientist of FDA, Dr. Namandjé N. Bumpus, wherein she granted Intarcia's request under 21 CFR 12.32(b)(3)(ii) for a public hearing before an advisory committee in lieu of a formal evidentiary hearing. Intarcia requested a public hearing before an advisory committee on CDER's proposal to refuse approval of Intarcia's NDA for ITCA 650 (see Docket No. FDA-2021-N-0874).

**Attendance:**

**EMDAC Members Present (Voting)**: Robert Alan Greevy, Jr., PhD; Rita R. Kalyani, MD, MHS; Cecilia C. Low Wang, MD *(Chairperson)*; Thomas Wang, MD

**EMDAC Members Not Present (Voting)**: Michael Blaha, MD, MPH; Matthew T. Drake MD, PhD

**EMDAC Member Present (Non-Voting)**: Gary Meininger, MD (*Industry Representative*)

**Temporary Members (Voting)**: Barbara Berney (*Patient Representative*); Erica Brittain, PhD; Kenneth D. Burman, MD; David W. Cooke, MD; Jill P. Crandall, MD; Yadin B. David, EdD, PE, CCE (GP); Brendan M. Everett, MD, MPH; Leonid Kagan, PhD; Marvin A. Konstam, MD; Kashif M. Munir, MD; Patrick H. Nachman, MD, FASN; Martha Nason, PhD; Connie Newman, MD; Thomas J. Weber, MD; and Peter W.F. Wilson, MD

**FDA Participants (Non-Voting):** Peter Stein, MD; Hylton Joffe, MD; Lisa Yanoff, MD; John Sharretts, MD; Patrick Archdeacon, MD; Michelle Carey, MD; Justin Penzenstadler, PharmD; David Wolloscheck, PhD; Edwin Chow, PhD; Wenda Tu, PhD

**Designated Federal Officer (Non-Voting)**: LaToya Bonner, PharmD

**Open Public Hearing Speakers Present:** William Dirkes, MD; Robert Busch, MD, FACE; Lisa Connery, MD; Thomas Blevins, MD; Kelly Kunik; Samir Aurora, MD; Rebecca Delong; Steve Edelman; Esther Tarango; Douglas K. Logan; Douglas Scott Denham (Flourish Research); Brendan Jones; Ramon Beltran; Marie Romo; Kelly Close (Close Concerns); Michael Abrams, PhD (Public Citizen); Richard Wood and Alison Zeng (dQ&A)

***The agenda was as follows:***

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| Call to Order | **Cecilia Low Wang, MD**<br>Chairperson, EMDAC |
| Introduction of Committee and Conflict of Interest Statement | **LaToya Bonner, PharmD**<br>Designated Federal Officer, EMDAC |
| FDA Opening Remarks | **Patrick Archdeacon, MD**<br>Deputy Director<br>Division of Diabetes, Lipid Disorders, and Obesity (DDLO)<br>Office of Cardiology, Hematology, Endocrinology, and Nephrology (OCHEN)<br>Office of New Drugs (OND), CDER, FDA |
| **APPLICANT PRESENTATIONS** | **Intarcia Therapeutics (an i2o Business Unit)** |
| Introduction | **Kurt Graves**<br>Chairman, President, CEO<br>Intarcia Therapeutics (an i2o Business Unit) |
| Clinical Efficacy | **Daniel Drucker, MD, FRS, FRCPC, OC**<br>Senior Scientist<br>Lunenfeld-Tanenbaum Research Institute<br>Mount Sinai Hospital<br>Professor of Medicine<br>University of Toronto |
| Clinical Safety | |
| 1. Acute Kidney Injury (AKI) | **Daniel Drucker, MD, FRS, FRCPC, OC** |

| | |
|---|---|
| 2. Major Adverse Cardiovascular Events (MACE) | **Philip Sager, MD, FACC, FAHA, FHRS**<br>Adjunct Professor<br>Stanford University School of Medicine<br>Member, Executive Committee<br>Cardiac Safety Research Consortium |
| 3. Clinical Validation of Device In Vitro Release (IVR) | **Kurt Graves** |
| Benefit/Risk & Conclusions | **Kurt Graves** |

**BREAK**

**FDA PRESENTATIONS**

| | |
|---|---|
| ITCA 650 (exenatide in DUROS) Device Review Conclusions | **David Wolloscheck, PhD**<br>Assistant Director<br>Division of Drug Delivery, General Hospital Devices, and Human Factors<br>Office of Gastrorenal, Ob/Gyn, General Hospital and Urology Devices (OHT3)<br>Office of Product Evaluation and Quality (OPEQ)<br>Center for Devices and Radiological Health (CDRH)<br>FDA |
| Clinical Pharmacology Assessment of ITCA 650 | **Edwin Chiu Yuen Chow, PhD**<br>Clinical Pharmacology Team Leader<br>Division of Cardiometabolic and Endocrine Pharmacology (DCEP)<br>Office of Clinical Pharmacology (OCP)<br>Office of Translational Sciences (OTS), CDER, FDA |
| Overview of Sources of Clinical Data for Efficacy and Safety | **Patrick Archdeacon, MD**<br>Deputy Director<br>DDLO, OCHEN, OND, CDER, FDA |
| Efficacy Review of Studies CLP-103 and CLP-105 | **Wenda Tu, PhD**<br>Statistical Reviewer<br>Division of Biometrics II (DBII)<br>Office of Biostatistics (OB) |
| Clinical Safety Presentation and Summary of CDER's Overall Conclusions | **Michelle Carey, MD, MPH**<br>Associate Director for Therapeutic Review<br>DDLO, OCHEN, OND |
| Clarifying Questions | |

**LUNCH**

**OPEN PUBLIC HEARING**

Questions to the Committee/Committee Discussion

**BREAK**

Questions to the Committee/Committee Discussion

**ADJOURNMENT**

***Questions to the Committee:***

1. **DISCUSSION:** Discuss your assessment of the safety profile of ITCA 650 and whether the safety profile of the ITCA 650 drug-device combination product has been adequately characterized based on available data:
    a. with respect to acute kidney injury
    b. with respect to cardiovascular safety
    c. with respect to overall safety

    ***Committee Discussion****:*

    *With respect to acute kidney injury (AKI), Committee members expressed concerns about the imbalance in AKI. Although multiple Committee members noted the low incidence of AKI, there were concerns expressed about this risk being increased while on metformin, or ACE inhibitors, or ARBs, which are all therapies that patients with type 2 diabetes are likely to be taking. One Committee member noted the concerning safety signal for acute kidney injury especially given the fact that the proportion of patients in the trials with renal insufficiency was lower than in trials for other GLP1 receptor agonists. One Committee member noted that the characterization of AKI is limited by the number of events that occurred in the population that was studied: she noted that there appears to be an imbalance that does not favor the drug-device combination product, but that the absolute risk was relatively low. One Committee member stated he had serious concerns about the acute kidney injury signal because the signal was detected in clinical trials with a low proportion of participants with significant chronic kidney disease, leading to a concern that rates of acute kidney injury would be higher in a real-world clinical treatment setting. One Committee member stated that the AKI risk needs to be resolved and indicated this should be done by developing a strategy to mitigate the risk and testing it out.*

    *Regarding cardiovascular safety, the Committee members expressed concerns about the MACE point estimate being above 1 and overall felt that the cardiovascular safety signal needs to be further investigated before consideration for approval. One Committee member noted that he thinks the sponsor and FDA are in reasonable agreement on the fact that another trial is needed to characterize cardiovascular safety and the only question is whether*

*the trial should be pre-approval or post-approval, a position that was endorsed by another Committee member. One Committee member stated she was "torn" about the cardiovascular signal because the upper bound of the 95% confidence interval of 1.8 is prespecified but noted that "there were quite a few trials that were similar length of follow-up that really did have much better results." One Committee member noted his participation in previous EMDAC discussion of cardiovascular risk assessment, stating "having been there – it was not the intent to say below 1.8 is a go-home-free card. It's necessary but not sufficient." Another Committee member noted that the estimate is substantially in the wrong direction and there is a responsibility to rule out that potential signal of harm.*

*In terms of overall safety, the Committee expressed concerns related to AKI and cardiovascular risk, and all-cause mortality was also mentioned. One Committee member stated that her main concern was with marked intra-subject variability in measured levels of exenatide even at timepoints chosen to be "steady-state", with subsequent impact on risk for GI adverse effects and resulting decreased renal function. A few Committee members expressed concerns about the lack of information about glycemic excursions and rate of hyper- and hypoglycemia with concerns about variability in the release of the drug. One Committee member stated her larger concern is overall safety in that we don't really have a sense of variability in glucose excursions that may reflect variability in drug delivery. Another Committee member stated that ITCA 650 is different from previous GLP-1 receptor agonists that have demonstrated consistent delivery, so gathering more data would be helpful to address these concerns.*

*Please see the transcript for details of the Committee's discussion.*

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

***Committee Discussion**:*

*Regarding the Committee's assessment of the benefit-risk balance of ITCA 650 for the indication to improve glycemic control in patients with type 2 diabetes, in general, the Committee members felt that the benefits of ITCA 650 did not outweigh the risks. The Committee members expressed general agreement that the product had demonstrated benefit in terms of improved A1C control and weight loss. The Committee members also acknowledged the potential adherence benefit of ITCA 650, which delivers exenatide via an implantable device, but also noted that adherence is a complex problem and there is a lack of evidence for improved adherence with this device. Committee members also commented on the moving testimonies during the open public hearing but noted the availability of other options for type 2 diabetes treatment, including several that reduce cardiovascular risk and risk for kidney outcomes. The Committee members also discussed concerns regarding unresolved safety signals, concerns about the potential for dosing variabilities (e.g., inconsistent and inaccurate dosing by the device), and concerns about the lack of mechanisms in place to alert the patient or provider about device performance. One Committee member commented that the variable drug delivery was akin to variable adherence with the drug. One Committee member commented that there is a place for ITCA 650 or something similar, but the problems with variable delivery would need to be*

*addressed, and it would need to be with more complete information about risk. Please see the transcript for details of the Committee's discussion.*

3. **VOTE:** Based on the available data has the Applicant demonstrated that the benefits of the ITCA 650 drug-device combination product outweigh its risks for the treatment of T2DM?
    a. If yes, explain your rationale.
    b. If no, explain your rationale and comment on additional data that could be provided to demonstrate the benefits outweigh the risks.

**Vote Result:** Yes: 0 No: 19 Abstain: 0

***Committee Discussion:*** *The Committee unanimously voted "No", concluding that, based on available data, the Applicant did not demonstrate that the benefits of the ITCA 650 drug-device combination product outweigh its risks for the treatment of T2DM. The Committee members mentioned uncertainty about AKI and cardiovascular safety, as well as the variability in drug delivery as being the greatest concerns. Additional studies suggested included a cardiovascular and renal outcomes trial with rigorous adjudication of key endpoints using an active comparator (i.e., another GLP-1 receptor agonist) and enrolling more patients with advanced chronic kidney disease (one Committee member proposed studying a patient population with a GFR range of 45 to 75). One Committee member recommended clarifying the question surrounding AKI with an active comparator trial with another GLP-1 agonist, indicating that this could support addressing cardiovascular safety in a post marketing study. Another Committee member similarly recommended a safety study that could be "fairly short" to figure out the best mitigation strategy to reduce adverse kidney effects before undertaking a CVOT. A third Committee member recommended more clinical data to better characterize the potential glycemic variation by means of CGM or other methods and perhaps a short-term trial to assess renal effects and mitigation strategies. A fourth Committee member stated that "While I see the benefits of shorter-term trials focused on specific renal and pharmacokinetic questions, ultimately, I come to the unavoidable conclusion that a larger and more definitive cardiovascular outcomes study is necessary to address both renal and cardiovascular safety, and it would be best to do that in a preapproval setting." A fifth Committee member recommended a cardiovascular outcomes trial that is specifically focused with prespecified renal outcomes as well, with rigorous adjudication by an independent endpoints committee of kidney specialists. Other suggestions were to include older adults with diabetes, including a run-in period with an injected GLP1 receptor agonist to select patient who tolerate the therapy prior to implanting the drug-device combination, more collection of GLP-1 receptor agonist levels to demonstrate release rates, more complete case reporting of adverse events of interest, an assessment of adherence, and use of continuous glucose monitoring. Multiple Committee members endorsed the value of continuous glucose monitoring to provide important data about hypoglycemia and glycemic variability as a means of addressing concerns that the device may be delivering exenatide inconsistently. Please see the transcript for details of the Committee's discussion.*

The meeting was adjourned at approximately 5:32 p.m. ET.