Effects of Mifepristone in People With Difficult-to-Control T2D and Hypercortisolism on GLP-1 RAs

Lance A. Sloan,[1] Vanita R. Aroda, Robert S. Busch, John B. Buse, Elena A. Christofides, Ralph A. DeFronzo, Bradley Eilerman, Vivian Fonseca, Yehuda Handelsman, Yu Mi Kang, John C. Parker, Athena Philis-Tsimikas, Richard Pratley, Julio Rosenstock, Michael H. Shanik, Guillermo Umpierrez, Austin L. Hand, Tina K. Schlafly, and Daniel Einhorn

[1]Texas Institute for Kidney and Endocrine Disorders, Lufkin, TX

CATALYST

Study of Hypercortisolism in Patients with Difficult-to-Control Type 2 Diabetes

Disclosures

Lance A. Sloan

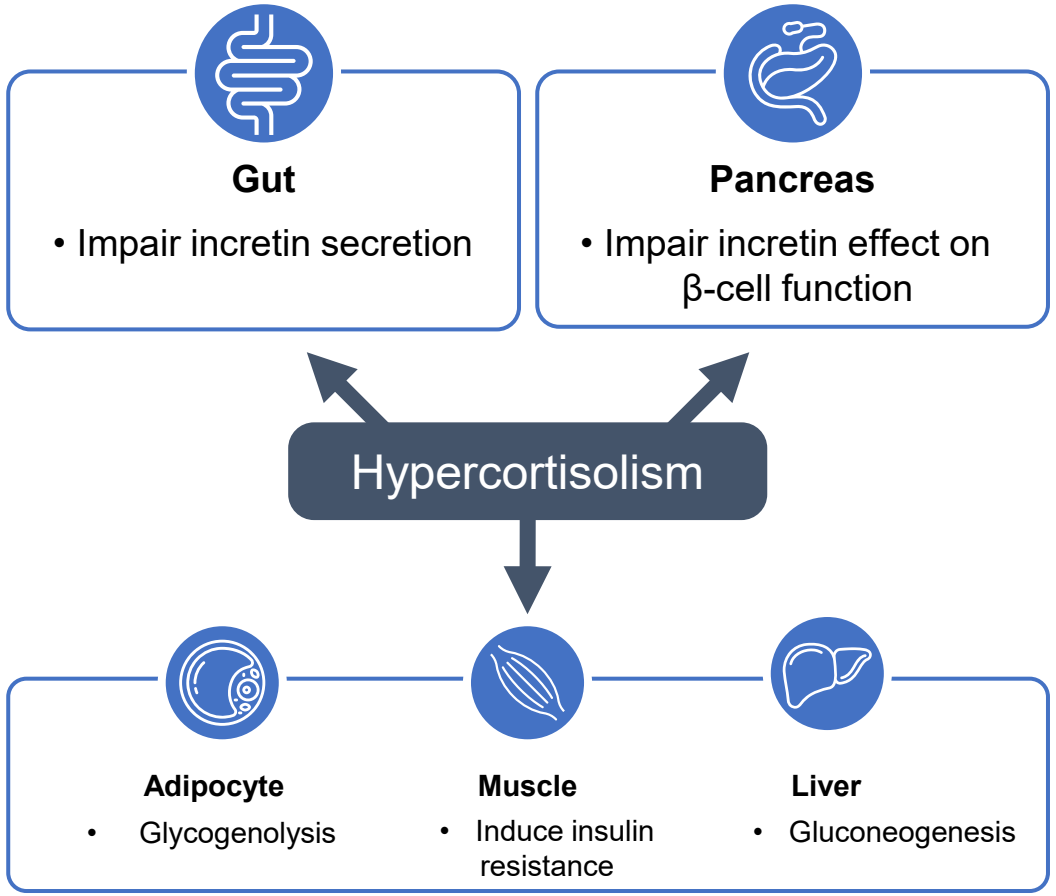
- Advisory board with AstraZeneca, Boehringer Ingelheim, Corcept Therapeutics, Inc., Crinetics, Idorsia, Lilly, Novo Nordisk, and Pfizer
- Speaker bureau with Ascendis, AstraZeneca, Bayer, Boehringer Ingelheim, Corcept Therapeutics, Inc., Lilly, Madrigal, Pfizer, Sanofi, and Xeris
- Clinical research for Amgen, Boehringer Ingelheim, Corcept Therapeutics, Inc., Janssen, Lilly, Merck, Novo Nordisk, and Sanofi

Permission is granted to take pictures.

CATALYST Study Background

- CATALYST was the largest prospective study to date assessing the prevalence of endogenous hypercortisolism (HC) in US adults with difficult-to-control T2D, finding a prevalence of 23.8%[1]
- The randomized, double-blind treatment phase of CATALYST evaluated mifepristone vs placebo for treating HC in people with difficult-to-control T2D[2]
- In this sub-analysis from the treatment phase, we assessed the effects of mifepristone treatment in CATALYST participants taking incretin mimetics (GLP-1 RAs or tirzepatide)

Mechanisms Through Which HC May Interfere with Glucose Homeostasis[3]



CATALYST is registered as NT05772169.
GLP-1 RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes.
1. Buse JB, et al. *Diabetes Care.* 2025:dc242841. 2. DeFronzo RA, et al. *Diabetes Care.* 2025;48(12):2036-2044. 3. DeFronzo RA, Auchus RJ. *Diabetes.* 2025;74(12):2168-2217.

Definitions in CATALYST

Difficult-to-Control Type 2 Diabetes

- HbA1c 7.5%–11.5% and at least one of the following criteria[1]:
  - ≥3 glucose-lowering medications
  - Taking insulin and any other glucose-lowering medication(s)
  - ≥2 glucose-lowering medications and having ≥1 microvascular or macrovascular complication(s)
  - Taking ≥2 glucose-lowering and ≥2 blood pressure–lowering medications

Endogenous Hypercortisolism

- Post 1 mg DST cortisol >1.8 µg/dL and
- Dexamethasone ≥140 ng/dL

Common causes of false-positive DSTs were excluded

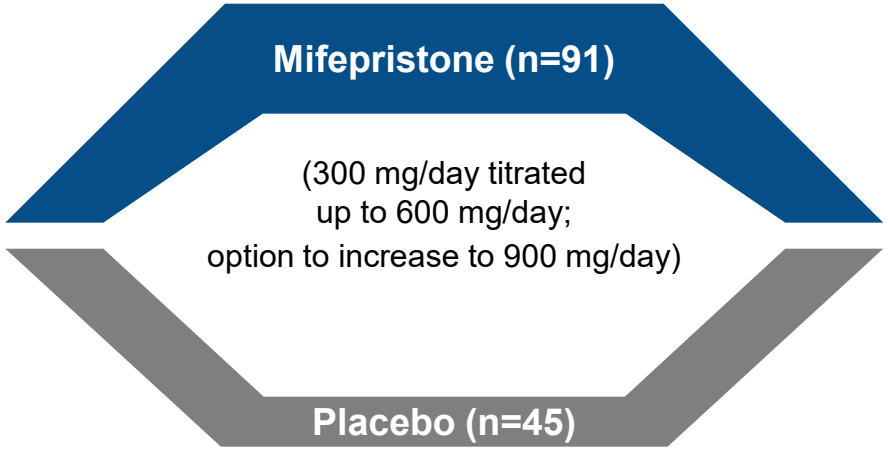
ACTH, adrenocorticotropic hormone; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; HbA1c, hemoglobin A1c.

1. DeFronzo RA, et al. *Diabetes Care.* 2025;48(12):2036-2044. 2. Fassnacht M, et al. *Eur J Endocrinol.* 2023;189(1):G1-G42. 3. Nieman LK, et al. *J Clin Endocrinol Metab*. 2008;93(5):1526-1540. 4. Zeiger MA, et al. *Endocr Pract*. 2009;15(5):450-453. 5. Chiodini I, et al. *J Endocr Soc*. 2019;3(5):1097-1109.

CATALYST Treatment Phase: Study Design and Current Analysis

Primary endpoint: Change in HbA1c from baseline to week 24

2:1 Randomization
Stratified by adrenal imaging abnormality (yes/no)



24 weeks

Persons with difficult-to-control T2D[a] and hypercortisolism[b] meeting Part 2 inclusion and exclusion criteria (N=136)

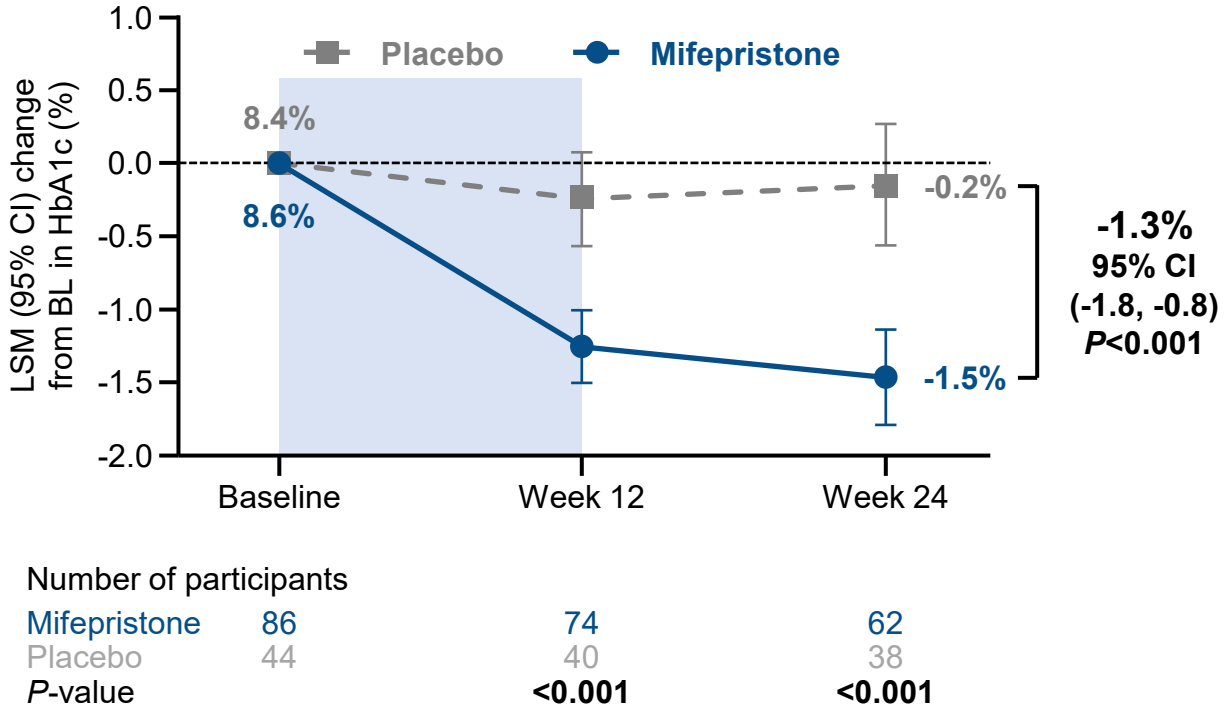
Current Analysis

Incretin mimetic subgroup (N=71): Participants who took incretin mimetics before the study and for ≥80% of the study duration

[a]HbA1c 7.5%–11.5% on multiple glucose-lowering medications. [b]Cortisol >1.8 µg/dL after 1-mg overnight dexamethasone suppression test.
HbA1c, hemoglobin A1c; GLP-1 RA, glucagon-like peptide-1 receptor agonist; T2D, type 2 diabetes.
DeFronzo RA, et al. *Diabetes Care.* 2025;48(12):2036-2044.

CATALYST Primary Endpoint: Statistically and Clinically Significant Reduction in HbA1c Despite Medication Reductions/Discontinuation

Treatment Phase Primary Endpoint: Change in HbA1c



Number of participants			
Mifepristone	86	74	62
Placebo	44	40	38
P-value		**<0.001**	**<0.001**

Discontinuations/Dose-Reductions in Glucose-Lowering Medications by Week 12 in Overall Population

	Mifepristone n/N[a] (%)	Placebo n/N[a] (%)
Long-acting insulin	32/65 (49.2)	3/23 (13.0)
Fast-acting insulin	10/33 (30.3)	2/19 (10.5)
Sulfonylureas	4/18 (22.2)	2/19 (10.5)
GLP-1 RAs	4/33 (12.1)	0/19 (0)
Tirzepatide	2/19 (10.5)	0/3 (0)
Metformin	1/67 (1.5)	0/33 (0)
SGLT2 inhibitors	0/56 (0)	1/27 (3.7)
Total	**53**	**8**

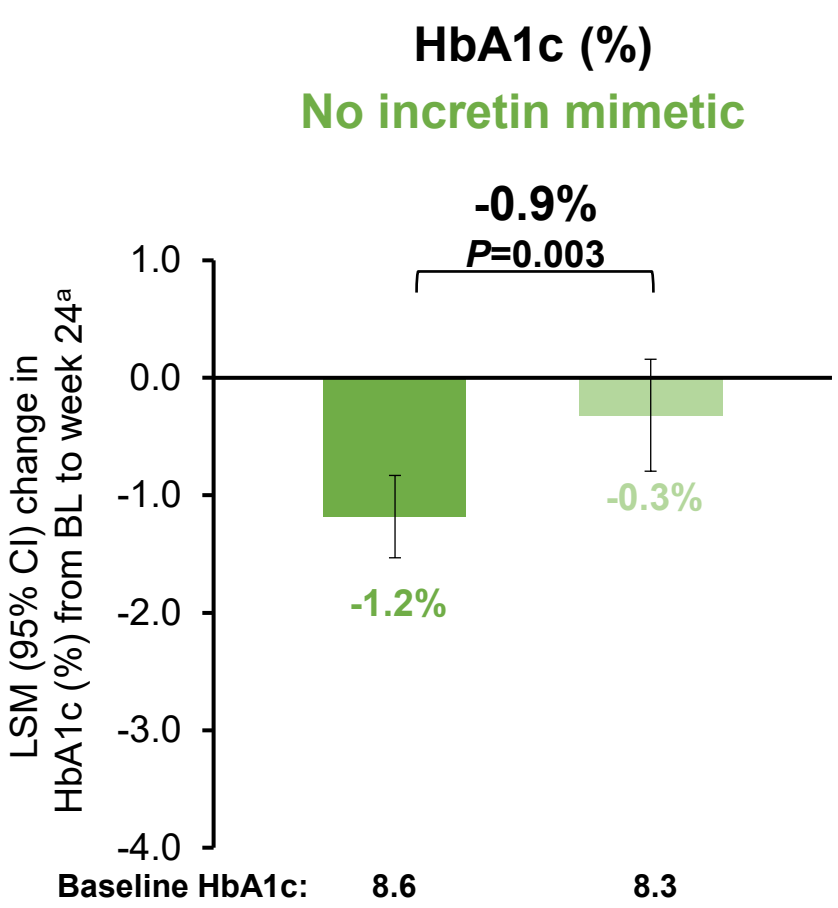
[a]N = the total number of patients taking each class of medication at baseline.
P-value for LSM difference between mifepristone and placebo.
BL, baseline; CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; LSM, least-squares mean; SGLT2, sodium-glucose cotransporter 2.
DeFronzo RA, et al. *Diabetes Care.* 2025;48(12):2036-2044.

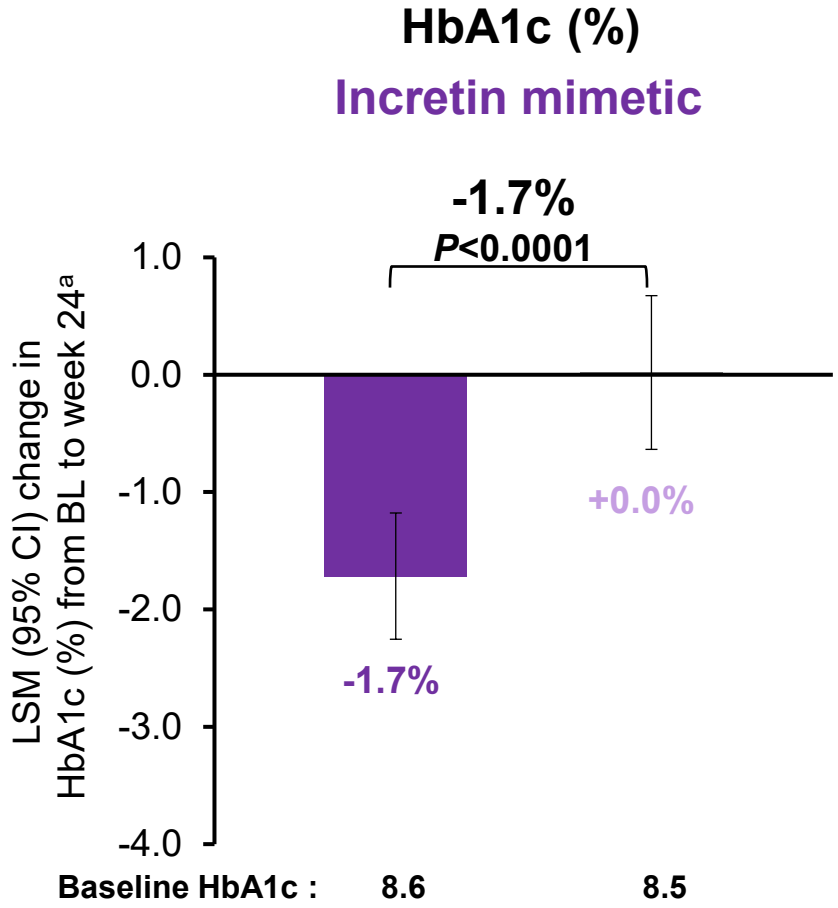
Baseline Characteristics

	Overall population		No incretin mimetic		Incretin mimetic	
	Mifepristone (n=91)	Placebo (n=45)	Mifepristone (n=45)	Placebo (n=20)	Mifepristone (n=46)	Placebo (n=25)
Age, years, mean (SD)	62.9 (8.9)	63.8 (11.5)	62.9 (9.0)	67.6 (8.0)	62.8 (8.9)	60.9 (13.0)
Male, %	59.3	64.4	55.6	60.0	63.0	68.0
Race, %						
White	78.0	86.7	62.2	85.0	93.5	88.0
Black or African American	17.6	11.1	28.9	10.0	6.5	12.0
Other[a]	4.4	2.2	8.9	5.0	0	0
Ethnicity, %						
Hispanic or Latino	5.5	8.9	8.9	15.0	2.2	4.0
Not Hispanic or Latino	93.4	91.1	91.1	85.0	95.7	96.0
Body weight, kg, mean (SD)	99.7 (23.2)	97.4 (23.4)	92.0 (21.9)	92.7 (17.3)	107.2 (22.2)	101.2 (27.1)
Waist circumference, cm, mean (SD)	114.0 (17.5)	115.3 (18.2)	109.1 (18.2)	114.0 (13.8)	118.7 (15.4)	116.3 (21.4)
Body mass index, kg/m^2, mean (SD)	33.1 (7.3)	33.7 (8.2)	31.1 (6.4)	33.1 (7.4)	35.2 (7.6)	34.3 (9.0)
HbA1c, %, mean (SD)	8.6 (1.3)	8.4 (1.1)	8.6 (1.3)	8.3 (0.9)	8.6 (1.3)	8.5 (1.2)
Systolic blood pressure, mmHg, mean (SD)	125.0 (16.0)	125.4 (14.8)	124.9 (16.7)	127.5 (15.7)	125.2 (15.4)	123.7 (14.1)
Diastolic blood pressure, mmHg, mean (SD)	74.1 (9.1)	73.3 (9.4)	72.0 (8.4)	71.7 (12.0)	76.1 (9.4)	74.6 (6.8)

[a]Includes Asian, multiple, and other.
HbA1c, hemoglobin A1c; SD, standard deviation.

Mifepristone Significantly Decreased HbA1c in Participants With or Without Incretin Mimetic Use



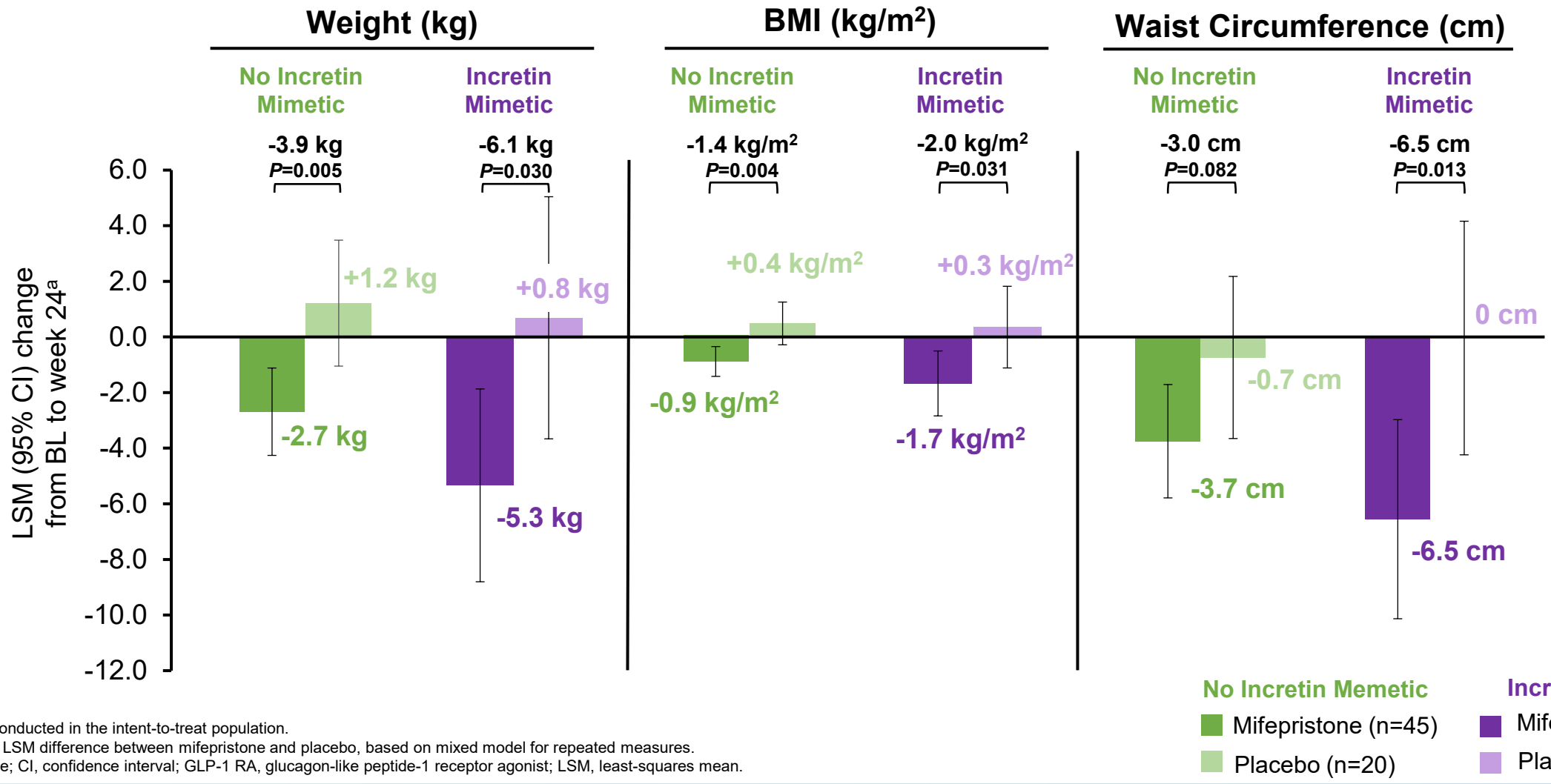


No Incretin Memetic
- Mifepristone (n=45)
- Placebo (n=20)

Incretin Mimetic
- Mifepristone (n=46)
- Placebo (n=25)

[a]Analysis conducted in the intent-to-treat population.
P-value for LSM difference between mifepristone and placebo, based on mixed model for repeated measures.
BL, baseline; CI, confidence interval; HbA1c, hemoglobin A1c; LSM, least-squares mean; SD, standard deviation.

Mifepristone Significantly Reduced Weight, BMI, and Waist Circumference in Participants With and Without Incretin Memetics



[a]Analysis conducted in the intent-to-treat population.
P-value for LSM difference between mifepristone and placebo, based on mixed model for repeated measures.
BL, baseline; CI, confidence interval; GLP-1 RA, glucagon-like peptide-1 receptor agonist; LSM, least-squares mean.

Safety Profile Similar Between Incretin Mimetic Subgroups

n (%)[a]	Overall population		No incretin mimetic		Incretin mimetic	
	Mifepristone (n=91)	Placebo (n=43)	Mifepristone (n=45)	Placebo (n=18)	Mifepristone (n=46)	Placebo (n=25)
At least one TEAE event	86 (94.5)	36 (83.7)	43 (95.6)	15 (83.3)	43 (93.5)	21 (84.0)
At least one treatment-related AE	56 (61.5)	14 (32.6)	27 (60.0)	6 (33.3)	29 (63.0)	8 (32.0)
TEAEs leading to treatment discontinuation	26 (28.6)	1 (2.3)	13 (28.9)	0	13 (28.3)	1 (4.0)
Serious TEAE	29 (31.9)	2 (4.7)	17 (37.8)	0	12 (26.1)	2 (8.0)
Most common TEAEs[b]						
Hypokalemia	27 (29.7)	0	15 (33.3)	0	12 (26.1)	0
Fatigue	19 (20.9)	7 (16.3)	7 (15.6)	4 (22.2)	12 (26.1)	3 (12.0)
Nausea	19 (20.9)	5 (11.6)	8 (17.8)	3 (16.7)	11 (23.9)	2 (8.0)
Vomiting	14 (15.4)	3 (7.0)	5 (11.1)	0	9 (19.6)	3 (12.0)
Peripheral edema	14 (15.4)	1 (2.3)	7 (15.6)	1 (5.6)	7 (15.2)	0
Headache	11 (12.1)	5 (11.6)	5 (11.1)	3 (16.7)	6 (13.0)	2 (8.0)
Dizziness	10 (11.0)	3 (7.0)	6 (13.3)	3 (16.7)	4 (8.7)	0
Diarrhea	10 (11.0)	3 (7.0)	3 (6.7)	0	7 (15.2)	3 (12.0)

[a]Results shown for the safety population, defined as participants who received ≥1 dose of study drug. [b]TEAEs occurring in ≥15% of participants.
AE, adverse event; TEAE, treatment-emergent AE.

Summary and Conclusions

1 Mifepristone significantly reduced HbA1c in CATALYST	• In CATALYST, 23.8% of individuals with difficult-to-control T2D had hypercortisolism[1] • Mifepristone led to clinically and statistically significant improvements in HbA1c vs placebo (-1.3%, *P*<0.001)[2]
2 Excess cortisol may impair incretin response	• Excess cortisol may reduce the efficacy of incretin mimetics by disrupting the incretin system, impairing β-cell function, and inducing insulin and incretin resistance[3]
3 Mifepristone benefits are seen with or without incretin mimetic use	• In this subgroup analysis, mifepristone significantly improved HbA1c, weight, BMI, and waist circumference in participants with or without use of incretin mimetics • Decreases in HbA1c, weight, BMI, and waist circumference following mifepristone treatment were numerically larger in participants taking incretin mimetics compared with those not taking incretin mimetics
4 Treating HC is warranted in difficult-to-control T2D	• Cortisol-directed therapy appears to provide benefits that were not achievable with incretin mimetics alone in participants with HC • Cortisol-directed therapy is not intensification – it is re-direction of therapy toward an underling cause

BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HbA1c, hemoglobin A1c; HC, hypercortisolism; T2D, type 2 diabetes.

1. Buse JB, et al. *Diabetes Care.* 2025:dc242841. 2. DeFronzo RA, et al. *Diabetes Care.* 2025;48(12):2036-2044. 3. DeFronzo RA, Auchus RJ. *Diabetes.* 2025;74(12):2168-2217.

THANKS TO ALL WHO CONTRIBUTED TO CATALYST

The study participants and their families

The CATALYST investigators and their teams

- Andrew Ahmann
- Vanita R. Aroda
- Timothy Bailey
- Lawrence Blonde
- Robert S. Busch
- John B. Buse
- Margaret Chang
- Elena A. Christofides
- Ralph A. DeFronzo
- John Delgado
- Bradley Eilerman
- Juan Frias / David Guzman
- Adline Ghazi
- Yehuda Handelsman
- Stanley Hsia
- Steven E. Kahn
- Mark Kipnes
- Mark Leibowitz
- Sam Lerman
- Dragana Lovre
- Harold J. Miller
- Samer Nakhle
- Jonathan G. Ownby
- Jean Park
- John C. Parker
- Athena Philis-Tsimikas
- Rodica Pop-Busui / Richard J. Auchus
- Pratibha Rao
- Michael H. Shanik
- Lance A. Sloan
- Ronald S. Swerdloff
- Guillermo Umpierrez
- Matthew Wenker
- Kathleen Wyne
- Michael Zimmerman
- Julio Rosenstock / Dan Lender

Scan the QR code for a copy of the presentation.