# Final Results of the CATALYST Trial

Ralph A. DeFronzo,[1] Vivian Fonseca,[2] Vanita R. Aroda,[3] Richard J. Auchus,[4] Timothy Bailey,[5] Irina Bancos,[6] Robert S. Busch,[7] John B. Buse,[8] Elena A. Christofides,[9] Bradley Eilerman,[10] James W. Findling,[11] Yehuda Handelsman,[12] Steven E. Kahn,[13] Harold J. Miller,[14] Jonathan G. Ownby,[15] John C. Parker,[16] Athena Philis-Tsimikas,[17] Richard Pratley,[18] Julio Rosenstock,[19] Michael H. Shanik,[20] Lance A. Sloan,[21] Guillermo Umpierrez,[22] Samir Shambharkar,[23] Iulia Cristina Tudor,[23] Tina K. Schlafly,[23] and Daniel Einhorn,[23] on behalf of the CATALYST Investigators

[1]University of Texas Health Science Center at San Antonio and Texas Diabetes Institute, San Antonio, TX; [2]Tulane University, New Orleans, LA; [3]Brigham and Women's Hospital, Harvard Medical School, Boston, MA; [4]University of Michigan, Ann Arbor, MI; [5]Headlands Research AMCR Institute, Escondido, CA; [6]Mayo Clinic, Rochester, MN; [7]Albany Medical College, Community Endocrine Group, Albany, NY; [8]University of North Carolina School of Medicine, Chapel Hill, NC; [9]Endocrinology Associates, Columbus, OH; [10]St. Elizabeth Physicians, Covington, KY; [11]Medical College of Wisconsin, Milwaukee, WI; [12]Metabolic Institute of America, Tarzana, CA; [13]VA Puget Sound Health Care System and University of Washington, Seattle, WA; [14]NOLA Care Clinical Research Center, Covington, LA; [15]Atlanta Diabetes Associates, Atlanta, GA; [16]Accellacare Research, Wilmington Health, Wilmington, NC; [17]ScrippsWhittier Diabetes Institute, Scripps Health, La Jolla, CA; [18]AdventHealth Translational Research Institute Orlando, Orlando, FL; [19]Velocity Clinical Research at Medical City Dallas, Dallas, TX; [20]Endocrine Associates of Long Island, Smithtown, NY; [21]Texas Institute for Kidney and Endocrine Disorders, Lufkin, TX; [22]Emory School of Medicine, Emory University, Atlanta, GA; [23]Corcept Therapeutics Incorporated, Redwood City, CA

Scan QR code to access poster

Scan QR code to access publication

## SUMMARY & CONCLUSIONS


- In a cohort with difficult-to-control type 2 diabetes (T2D) and hypercortisolism, mifepristone resulted in **clinically & statistically significant improvements in** hemoglobin A1c (**HbA1c**) and other comorbidities
  - Comparable reductions in HbA1c were observed in participants with and without adrenal imaging abnormalities
- Adverse events were consistent with mifepristone's known safety profile
  - The most common adverse events were consistent with glucocorticoid withdrawal syndrome
  - Hypokalemia may be addressed by proactive initiation of a potassium-sparing diuretic (eg, spironolactone) in clinical practice (as opposed to a double-blind trial)
- **Key takeaway: In individuals with inadequately controlled T2D and hypercortisolism, cortisol-directed medical therapy with mifepristone significantly reduced HbA1c**


## BACKGROUND

- Results from Part 1 of the CATALYST trial (NCT05772169), the largest prospective study to date assessing the prevalence and characteristics of individuals with hypercortisolism among those with inadequately controlled T2D, found a hypercortisolism prevalence of 24% in this population[1]
- Among the available pharmacologic treatments for hypercortisolism, the glucocorticoid receptor antagonist mifepristone (Korlym®, Corcept Therapeutics Incorporated) is the only one indicated specifically for treating hyperglycemia secondary to endogenous hypercortisolism in adult patients with T2D or glucose intolerance who have failed surgery or are not candidates for surgery[2]
  - Mifepristone was approved by the Food and Drug Administration based on 50 patients from the pivotal SEISMIC study, a phase 3, open-label, 24-week, multicenter study demonstrating glycemic improvements with mifepristone treatment[3]

## AIM

- To report results from Part 2 of CATALYST, where individuals who were identified to have hypercortisolism in the prevalence phase and met additional inclusion criteria were randomized to treatment with mifepristone or placebo

## METHODS

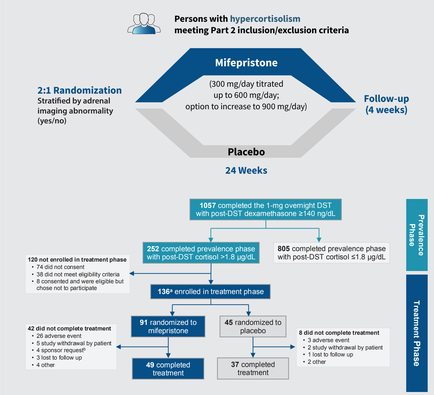
### Study Design

- CATALYST Part 2 was a double-blind, phase 4 study to evaluate the efficacy and safety of mifepristone in adults aged 18 to 80 years with difficult-to-control T2D and hypercortisolism
  - Difficult-to-control T2D was defined as HbA1c 7.5% to 11.5% despite taking multiple glucose-lowering medications with or without micro-/macrovascular complications or taking multiple blood pressure-lowering medications[1]
  - Hypercortisolism was defined as post–1-mg dexamethasone suppression test (DST) cortisol >1.8 µg/dL (50 nmol/L), with adequate dexamethasone levels ≥140 ng/dL[1]
  - Participants with common causes of false-positive DST test results (eg, use of oral contraceptive pills; excessive alcohol consumption) were excluded

## METHODS

- Participants were randomly assigned in a 2:1 ratio to receive mifepristone or placebo; randomization was stratified by the presence/absence of an adrenal abnormality on computed tomography scan (**Figure 1**)
- The primary endpoint was the change in HbA1c from baseline to Week 24 in participants treated with mifepristone vs placebo

**Figure 1. CATALYST Part 2 Study Design**




[a]Four participants did not meet all inclusion criteria but were enrolled in the treatment phase. [b]Reasons for not completing treatment due to sponsor request included: not meeting inclusion/exclusion criteria (n=2), life events preventing the participant from continuing in the study (n=1), and adverse event (n=1; worsening fatigue and elevated thyroid stimulating hormone).

DST, 1-mg dexamethasone suppression test.

## RESULTS: TREATMENT PHASE[4]

- 136 participants were enrolled and randomly assigned to mifepristone (n=91) or placebo (n=45)
- Baseline characteristics were similar to those identified to have hypercortisolism in the prevalence phase who did not enroll in the treatment phase (**Table 2**)

**Table 2. Demographics and Baseline Characteristics**

| Characteristic | Mifepristone (n=91) | Placebo (n=45) | Did Not Enroll in Treatment Phase[a] (n=118) |
|---|---|---|---|
| Age, years, mean (SD) | 62.9 (8.9) | 63.8 (11.5) | 64.3 (9.5) |
| Male, n (%) | 54 (59.3%) | 29 (64.4%) | 60 (50.8%) |
| Race, n (%) | | | |
| White | 71 (78.0%) | 39 (86.7%) | 79 (66.9%) |
| Black or African American | 16 (17.6%) | 5 (11.1%) | 34 (28.8%) |
| Other[b] | 4 (4.4%) | 1 (2.2%) | 5 (4.2%) |
| Ethnicity, n (%) | | | |
| Hispanic or Latino | 5 (5.5%) | 4 (8.9%) | 12 (10.2%) |
| Not Hispanic or Latino | 85 (93.4%) | 41 (91.1%) | 106 (89.8 %) |
| Abnormal adrenal CT scan, n (%) | 25 (27.5%) | 13 (28.9%) | N/A[c] |
| Body weight, kg, mean (SD) | 99.7 (23.21) | 97.4 (23.43) | 95.4 (24.2) |
| Waist circumference, cm, mean (SD) | 114.0 (17.45) | 115.3 (18.24) | 112.8 (17.4) |
| Body mass index, kg/m², mean (SD) | 33.1 (7.31) | 33.7 (8.21) | 32.8 (7.9) |
| HbA1c, %, mean (SD) | 8.62 (1.27) | 8.41 (1.08) | 8.82 (0.97) |
| Systolic blood pressure, mmHg, mean (SD) | 125.0 (15.98) | 125.4 (14.78) | 128.3 (16.5) |
| Diastolic blood pressure, mmHg, mean (SD) | 74.1 (9.12) | 73.3 (9.44) | 74.3 (9.5) |

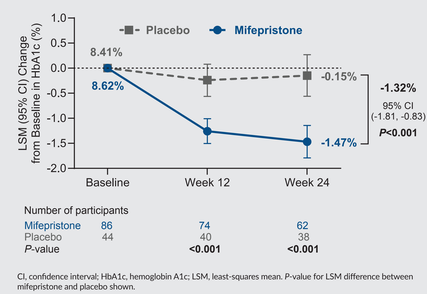
[a]Patients who completed prevalence phase with post-DST cortisol >1.8 µg /dL but did not enroll in treatment phase. The main reasons why participants did not enroll in the treatment phase were participant did not consent (n=74), not meeting eligibility criteria for the treatment phase (n=38), and participant decision (n=8). [b]Race category "Other" includes Asian, multiple, and other. [c]Not all participants completed the CT scan.

CT, computed tomography; HbA1c, hemoglobin A1c; SD, standard deviation.

## RESULTS: TREATMENT PHASE[4]

- Of the 91 participants randomized to mifepristone, 65 (71%) received 600 mg and of those, 28 (31%) received 900 mg mifepristone during the study
- Clinically and statistically significant reductions in HbA1c were seen in participants treated with mifepristone (**Figure 2**)
- The significant reduction of HbA1c occurred despite medication reduction/discontinuation (**Table 3**)
- 136 participants were enrolled and randomly assigned to mifepristone (n=91) or placebo (n=45)
- Baseline characteristics were similar to those identified to have hypercortisolism in the prevalence phase who did not enroll in the treatment phase (**Table 2**)

**Figure 2. Primary Endpoint Met: Significant Reduction in HbA1c, All Participants**




CI, confidence interval; HbA1c, hemoglobin A1c; LSM, least-squares mean. *P*-value for LSM difference between mifepristone and placebo shown.

**Table 3. Discontinuations/Dose Reductions in Glucose-Lowering Medications by Week 12**

| n/N[a] (%) | Mifepristone | Placebo |
|---|---|---|
| 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 |
| Tirzepatide | 2/19 (10.5%) | 0/3 |
| Metformin | 1/67 (1.5%) | 0/33 |
| SGLT2 inhibitors | 0/56 | 1/27 (3.7%) |
| **Total** | **53** | **8** |

[a]N indicates the number of participants taking a medication from the class at baseline. Dose decreases and discontinuations combined for insulin, sulfonylureas, GLP-1 RAs, and tirzepatide; discontinuations only for metformin and SGLT2 inhibitors.

GLP-1 RA, glucagon-like peptide-1 receptor agonist; SGLT2, sodium-glucose transport protein 2.

- Consistent improvement in HbA1c was seen in subgroup analyses in participants who completed the study and participants who received 900 mg of mifepristone for at least 28 consecutive days (**Table 4**)

**Table 4. HbA1c: Subgroup Analyses Support the Primary Endpoint**

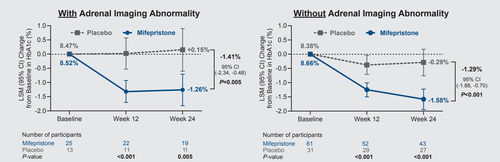
| HbA1c (%) | Mifepristone | Placebo | Difference from Placebo | *P*-value |
|---|---|---|---|---|
| **Participants who completed 24 weeks of treatment** | | | | |
| Baseline, mean (SD) [n] | 8.82 (1.33) [47] | 8.42 (1.02) [36] | — | — |
| Change from baseline to Week 24, LSM (95% CI) [n] | **-1.69** (-2.09, -1.30) [47] | -0.13 (-0.58, 0.32) [36] | **-1.56** (-2.12, -1.00) | **<0.001** |
| **Participants who received 3 tablets (900 mg mifepristone)** | | | | |
| Baseline, mean (SD) [n] | 9.10 (1.35) [24] | 8.62 (1.09) [25] | — | — |
| Change from baseline to Week 24, LSM (95% CI) [n] | **-2.01** (-2.63, -1.39) [23] | -0.16 (-0.76, 0.45) [25] | **-1.85** (-2.67, -1.04) | **<0.001** |

Analyses conducted to assess the robustness of the primary endpoint (tested in the intent-to-treat population). Analysis in participants who received 3 tablets includes those who received 3 tablets for at least 28 consecutive days. For all secondary endpoints, nominal p-values are displayed for testing the null hypothesis of no treatment effect.

CI, confidence interval; HbA1c, hemoglobin A1c, LSM, least-squares mean; SD, standard deviation.

- This was the first randomized, placebo-controlled study to show that hypercortisolism without an adrenal imaging abnormality responds to cortisol-directed pharmacologic treatment (**Figure 3**)

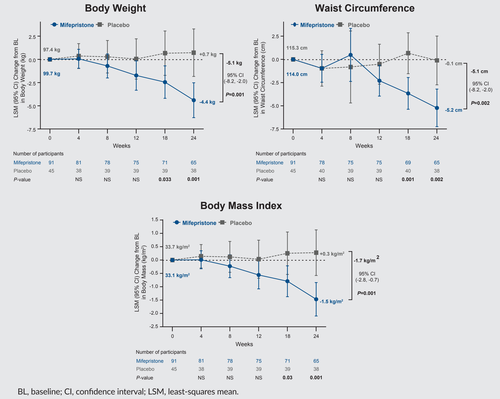
**Figure 3. Similar HbA1c Reductions in Participants With and Without Adrenal Imaging Abnormalities**




CI, confidence interval; CT, computed tomography; HbA1c, hemoglobin A1c; LSM, least-squares mean.

- By week 24, participants taking mifepristone had a 3.6% reduction in body weight compared to an increase of 0.3% in those taking placebo (**Figure 4**)
- Waist circumference decreased along with body weight, suggesting loss of primarily fat mass
- Body mass index decreases were continuing at study end

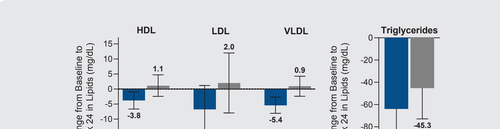
**Figure 4. Improvements in Body Weight, Waist Circumference, and Body Mass Index With Mifepristone**




BL, baseline; CI, confidence interval; LSM, least-squares mean.

- Lipids, which were normal or close to normal at baseline, decreased with mifepristone (**Figure 5**)

**Figure 5. Reductions in Lipids With Mifepristone**

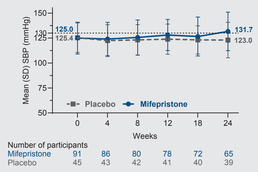



For all secondary endpoints, nominal *P*-values are displayed for testing the null hypothesis of no treatment effect.

BL, baseline; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LSM, least-squares mean; NS, not significant (*P*>0.05); SD, standard deviation; VLDL, very low-density lipoprotein.

- Systolic blood pressure (SBP) remained near target in the overall population and no changes from baseline were observed in participants with baseline SBP ≥130 mmHg (**Figure 6**)

**Figure 6. Effect of Mifepristone on Blood Pressure, All Participants**




SBP, systolic blood pressure; SD, standard deviation.

### Safety

- Overall TEAEs were mostly mild-to-moderate in severity; no grade 4 TEAEs observed (**Table 5**)
- TEAEs were manageable and consistent with mifepristone's known safety profile
- Hypokalemia, a known side-effect of mifepristone, was the most common adverse event
  - Due to overstimulation of the mineralocorticoid receptor
- Many of the most common TEAEs were consistent with glucocorticoid withdrawal, which can occur with any treatment for hypercortisolism, surgical or pharmacologic

**Table 5. Treatment-Emergent Adverse Events Reported in >10% of Participants**

| Preferred Term, n (%) | Mifepristone (n=91) | Placebo (n=43) |
|---|---|---|
| At least one TEAE event | 86 (94.5%) | 36 (83.7%) |
| At least one treatment-related AE | 56 (61.5%) | 14 (32.6%) |
| TEAEs leading to treatment discontinuation | 26 (28.6%) | 1 (2.3%) |
| Serious TEAE | 29 (31.9%) | 2 (4.7%) |
| Most common TEAEs | | |
| Hypokalemia | 27 (29.7%) | 0 |
| Fatigue | 19 (20.9%) | 7 (16.3%) |
| Nausea | 19 (20.9%) | 5 (11.6%) |
| Vomiting | 14 (15.4%) | 3 (7.0%) |
| Peripheral edema | 14 (15.4%) | 1 (2.3%) |
| Headache | 11 (12.1%) | 5 (11.6%) |
| Diarrhea | 10 (11.0%) | 3 (7.0%) |
| Dizziness | 10 (11.0%) | 3 (7.0%) |

AE, adverse event; TEAE, treatment-emergent adverse event.

## References


1. Buse JB, et al., *Diabetes Care.* 2025 [Online ahead of print]. https://doi.org/10.2337/dc24-2841
2. KORLYM® (mifepristone) 300 mg Tablets [prescribing information]. Redwood City, CA: Corcept Therapeutics Incorporated; September 2024.
3. Fleseriu M, et al. *J Clin Endocrinol Metab.* 2012;97(6):2039-49.
4. DeFronzo RA, et al., *Diabetes Care.* 2025 [Online ahead of print]. https://doi.org/10.2337/dc25-1055


## Acknowledgments

The authors want to thank all those who are participating in this study: The study participants and their families, the investigators, and the sponsor team. This study is sponsored by Corcept Therapeutics, Incorporated. Funding for editorial, design, and production support was provided by Corcept Therapeutics, Incorporated (Redwood City, CA, USA) to MedVal Scientific Information Services, LLC (Princeton, NY, USA).

## Disclosures

**RAD:** Research support: AstraZeneca, Boehringer Ingelheim; Speaker: AstraZeneca; Advisory board: AstraZeneca, Boehringer Ingelheim, Corcept Therapeutics, Intarcia, Novo Nordisk, Renalytix. **VF:** Research support: Corcept Therapeutics, Fractyl, Jaguar Gene Therapy; Consultant/speaker: Abbott, Asahi, Bayer, Boehringer Ingelheim, Corcept Therapeutics; Stock options: BRAVO4Health, Mellitus; Stock: Abbott, Amgen; Patents pending: BRAVO diabetes complications risk engine, PAX4 type 1 diabetes gene therapy. **VAR:** Research support: AstraZeneca, Boehringer Ingelheim, Corcept Therapeutics, Eli Lilly, Fractyl, Novo Nordisk, Pfizer, Rhythm, Sanofi, Servier; Consultant: Fractyl, Medtific, Novo Nordisk, Sanofi. **RJA:** Research support: Adrenas, Corcept Therapeutics, Crinetics, Mineralys, Neurocrine/Diurnal, Recordati, Spruce; Consultant/advisor: Acerand, Aspect, Astellas, Blue Earth, Corcept Therapeutics, Crinetics, Lundbeck, Neurocrine/Diurnal, Novo Nordisk, OMass, Quest, Recordati, Sparrow, Spruce, Xeris. **TB:** Research support: Abbott, BioDing, Corcept Therapeutics, Dexcom, Eli Lilly, Medtronic, Medtrum, Novo Nordisk, Sanofi, Senseonics, vTv; Consultant/advisor: Abbott, ACON, CeQur, HAGAR, Intuity, LifeScan, MannKind, Medtronic, Novo Nordisk, Perspirion, Sanofi, Sequel, Ypsomed. **IB:** Research support: HRA Pharma, Recordati; Consultant/advisor: Adrenas, AstraZeneca, Camurus, Corcept Therapeutics, Crinetics, Diurnal, HRA Pharma, Neurocrine, Novo Nordisk, Recordati, Sparrow, Spruce, Xeris. **ESB:** Grant: Corcept Therapeutics; Research support: Eli Lilly, Novo Nordisk, Novartis; Speaker: Amgen, AstraZeneca, Bayer, Eli Lilly, Novo Nordisk. **JBB:** Research support: Corcept Therapeutics, Dexcom, Novo Nordisk; Stock ownership: Glycsend, Mellitus, Metsera, Pendulum, Praetego, Stability; Advisor/consultant: Altimmune, Amgen, Antag, Afrikon, Aqua Medical, AstraZeneca, Boehringer-Ingelheim, CeQur, Corcept Therapeutics, Dexcom, Eli Lilly, Embecta, GentiBio, Glycsend, Insulet, Medtronic MiniMed, Mellitus, Metsera, Novo Nordisk, Pendulum, Praetego, Stability Health, Tandem, Terns, Vertex, Zealand. **EAC:** Research support: Chiesi, Eli Lilly, Novo Nordisk; Consultant/advisor: Accendis, Camurus, Crinetics; Speaker: Corcept Therapeutics, Eli Lilly, Recordati, Xeris. **BE:** Consultant/speaker: AbbVie; Corcept Therapeutics, Dexcom, Eli Lilly, Novo Nordisk. **JWF:** Consultant/advisor, Corcept Therapeutics, Diurnal. **YH:** Research support: Amgen, Applied, Corcept Therapeutics, Ionis, Eli Lilly, Merck, Regor; Consultant/advisor: Amgen, Applied, AstraZeneca, Bayer, Boehringer Ingelheim, Corcept Therapeutics, Esperion, MannKind, Merck, Merck-Pfizer, Novartis, Novo Nordisk, Sanofi; Speaker: Bayer, Esperion, Novo Nordisk. **SEK:** Research support: Corcept Therapeutics; Advisor/consultant: Abarrows, Amgen, AliPhys, Arij, Biomea Fusion, Eli Lilly, Merck, Neurimmune, Novo Nordisk; Stock: AliPhys. **HJM:** Nothing to disclose. **JGO:** Research support: AbbVie, Corcept Therapeutics; Speaker: Corcept Therapeutics. **JCP:** Consultant/advisor: Corcept Therapeutics, Insulet, Novo Nordisk. **APT:** Consultant/advisor: Bayer, Corcept Therapeutics, Dexcom, Eli Lilly, Medtronic, Novo Nordisk. Employee: Scripps Health; Research support: AbbVie, Corcept Therapeutics, Dexcom, Eli Lilly, Medtronic, National Center for Advancing Translational Science (NCATS), National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Novo Nordisk, Viking, vTv; Stock ownership: Ionis. **RP:** Consultant/advisor: Bayer, Corcept Therapeutics, Dexcom, Gainbertuna, Hanmi, Hengrui USA, Merck, Novo Nordisk, Pfizer, Rivus, Sanofi, Scohia, Sun; Research support: Hanmi, Metavention, Novo Nordisk, Powi; Speaker: Novo Nordisk. **JR:** Research support: Applied, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Intarcia, Merck, Novartis, Novo Nordisk, Oramed, Pfizer, Sanofi; Advisor: Applied, Boehringer Ingelheim, Eli Lilly, Hanmi, Intarcia, Novo Nordisk, Oramed, Sanofi, Scholar Rock, Structure, Terns, Zealand. **MHS:** Research support: AbbVie, Corcept Therapeutics, Novo Nordisk; Speaker: Abbott, Amgen, Bayer, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Xeris. **LAS:** Consultant/advisor: Bayer, Corcept Therapeutics, Novo Nordisk, Pfizer; Speaker: AstraZeneca, Bayer, Boehringer Ingelheim, Corcept Therapeutics, Eli Lilly, Sanofi, Pfizer. **GU:** Consultant/advisor: Corcept Therapeutics, Dexcom, GlyCare; Research support: Abbott, Bayer, Corcept Therapeutics, Dexcom, National Institutes of Health. **SS, ICT, TKS, DE:** Employment by and stock ownership in Corcept Therapeutics.

Presented at the Association of Diabetes Care and Education Specialists; August 8-11, Phoenix, AZ