Design of the CATALYST Trial and Prevalence Results

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85TH SCIENTIFIC SESSIONS

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Disclosures

Vanita R. Aroda:

- Institutional contracts: Amgen, Applied Therapeutics, AstraZeneca, Biomea, Boehringer Ingelheim, Corcept, Eli Lilly, Fractyl, Novo Nordisk, Pfizer, Recordati, Rhythm, Servier
- Consultant: Mediflix, Sanofi

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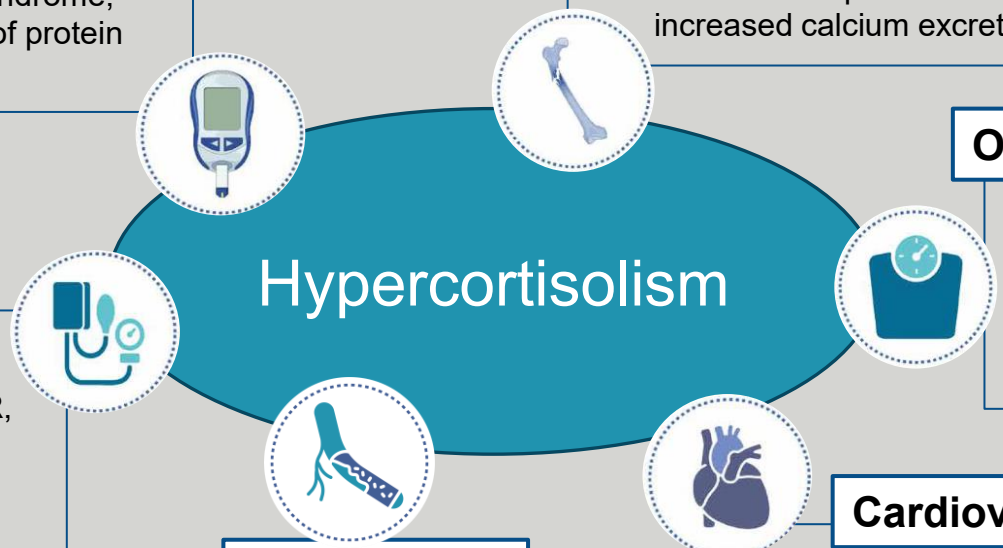
CATALYST Rationale



Diabetes mellitus

1. Stimulation of hepatic gluconeogenesis
2. Inhibition of hepatic & skeletal muscle insulin sensitivity
3. Coexistence of metabolic syndrome, dyslipidemia, & impairment of protein metabolism

Osteoporosis

1. ↓ Osteoblast number & function
2. Osteoclast stimulation → ↑ bone resorption
3. Osteocyte impairment & apoptosis
4. Coexistence of hypogonadism, inhibition of calcium resorption in the intestine, & increased calcium excretion in the kidneys

Obesity

1. ↑ Pre-adipocyte to adipocyte differentiation
2. ↓ Amino acid uptake
3. ↓ GLUT4 translocation
4. ↓ Lipogenesis & ↑ lipolysis
5. ↑ Appetite

High blood pressure

1. High cortisol levels saturate renal 11ß-HSD2 → cortisol can bind to the MR, leading to hypertension
2. ↑ Pressor response to angiotensin II
3. ↑ Sensitivity of ß-adrenoreceptor to catecholamines
4. ↑ Endothelin-1 levels

Dyslipidemia

1. ↑ Gluconeogenesis
2. ↑ Lipoprotein secretion & fatty acid synthesis
3. ↑ Hepatic glucose output & insulin resistance
4. ↑ Liver steatosis

Cardiovascular disease

1. ↑ Number of carotid plaques
2. Worse mid-wall systolic movement, left ventricular hypertrophy, & concentric remodeling
3. High prevalence of high blood pressure and other cardiovascular risk factors

M. Araujo-Castro et al. *Annales d'Endocrinologie.* 84 (2023):272–284. MR, mineralocorticoid receptor.

CATALYST Rationale

- **Hypercortisolism** is a recognized contributor to type 2 diabetes, metabolic syndrome, and cardiometabolic risk
- **Part 1:** What is the **prevalence of hypercortisolism** in individuals with difficult-to-control type 2 diabetes?
- **Part 2:** Can **treatment** with a cortisol-directed therapy improve glycemia in patients with type 2 diabetes?

M. Araujo-Castro et al. *Annales d'Endocrinologie*. 84 (2023):272–284. MR, mineralocorticoid receptor.

CATALYST

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

HyperCortisolism in PATients with Difficult-to-control Type 2 DiAbetes Despite Receiving Standard-of-care Therapies: PrevaLence and Treatment with KorlYm® (MifepriSTone)

A 2-part phase 4 study conducted at 36 sites in the US aiming to screen >1000 patients (NCT05772169)

Part 1 Prevalence Phase

Persons with difficult-to-control T2D

1-mg overnight DST

↓

Hypercortisolism
(post-DST cortisol >1.8 µg/dL with dexamethasone level ≥140 ng/dL)

↓

Further evaluation:
- Labs (ACTH, DHEAS, cortisol)
- Adrenal CT scan

Study Population: Key Inclusion

Protocol-defined "difficult-to-control type 2 diabetes:"

HbA1c 7.5–11.5% despite taking:

- ≥3 anti-hyperglycemic medications and/or
- Insulin and any other anti-hyperglycemic medications and/or
- ≥2 anti-hyperglycemic medications and presence of ≥1 micro- or macro-vascular complications and/or
- ≥2 anti-hyperglycemic and ≥2 anti-hypertensive medications

Study Population: Key Exclusion

Exclude common causes of false positive DST:

- Systemic glucocorticoids
- Pregnancy or lactation
- Use of oral contraceptives
- Hemodialysis or end-stage renal disease
- Severe untreated sleep apnea
- Excessive alcohol consumption
- Severe medical, surgical, or psychiatric illness
- Night shift worker

Primary aim of the prevalence phase: Assess the prevalence of hypercortisolism in a population with difficult-to-control T2D despite receiving standard-of-care therapies

ACTH, adrenocorticotropic hormone; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; HbA1c, hemoglobin A1c; T2D, type 2 diabetes.

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Defining Endogenous Hypercortisolism & Further Evaluation

- **Post–1-mg overnight dexamethasone suppression test (DST) cortisol >1.8 µg/dL**
- **Morning dexamethasone** ≥140 ng/dL to confirm the validity (suppression) of the 1-mg DST[1,2]
- **Lower DHEAS and plasma ACTH** suggest an ACTH-independent source of hypercortisolism[3,4]
- **Adrenal CT scan**

Primary aim of the prevalence phase: Assess the prevalence of hypercortisolism in a population with difficult-to-control T2D despite receiving standard-of-care therapies

ACTH, adrenocorticotropic hormone; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; LNSC, late-night salivary cortisol; T2D, type 2 diabetes; UFC, urinary free cortisol.

Screening Phase

Demographics and Baseline Characteristics

CATALYST enrolled a typical and diverse T2D population

	All participants (N=1,057)	Post-DST cortisol >1.8 µg/dL (hypercortisolism) (n=252)	Post-DST cortisol ≤1.8 µg/dL (n=805)	P-value for association with hypercortisolism[a]
Age, years, mean (SD)	60.7 (10.4)	63.8 (9.6)	59.8 (10.5)	**<0.0001**
Female, n (%)	479 (45.3%)	109 (43.3%)	370 (46.0%)	NS
Body mass index, kg/m^2, mean (SD)	33.5 (7.2)	33.1 (7.7)	33.7 (7.1)	NS
Waist circumference, inches, mean (SD)	112.7 (17.0)	113.5 (17.7)	112.5 (16.8)	NS
Ethnicity: Non-Hispanic/Latino[b], n (%)	802 (75.9%)	231 (91.7%)	571 (70.9%)	**<0.0001[c]**
Race, n (%)				
White	748 (70.8%)	187 (74.2%)	561 (69.7%)	NS[e]
Black or African American	201 (19.0%)	55 (21.8%)	146 (18.1%)	
Asian	47 (4.4%)	5 (2.0%)	42 (5.2%)	
Other[d]	61 (5.8%)	5 (2.0%)	56 (7.0%)	
HbA1c, %, mean (SD)	8.8 (1.0)	8.8 (1.1)	8.8 (1.0)	NS
SBP, mmHg, mean (SD)	127.6 (16.1)	127.4 (16.4)	127.6 (16.1)	NS
DBP, mmHg, mean (SD)	75.3 (9.8)	74.8 (9.5)	75.5 (9.9)	NS

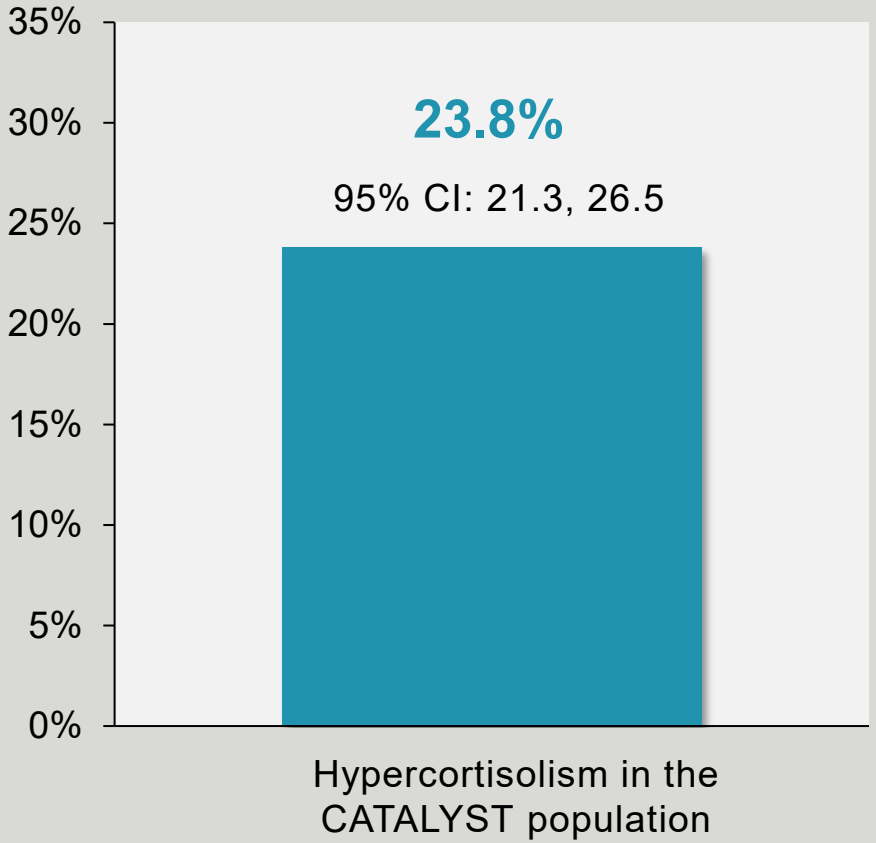
Buse, Kahn et al. *Diabetes Care* 2025:dc242841. [a]*P* value from a simple logistic regression model performed separately for each variable. [b]Includes participants with missing ethnicity data. [c]Comparison Non-Hispanic/Latino vs Hispanic/Latino. [d]Includes "American Indian or Alaska Native," "Native Hawaiian or Other Pacific Islander," "Multiple," "Other," and "Unknown." [e]Comparison non-White vs White.
DBP, diastolic blood pressure; DST, dexamethasone suppression test; HbA1c, hemoglobin A1c; NS, not significant; SBP, systolic blood pressure; SD, standard deviation; T2D, type 2 diabetes.

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

Screening Phase

Prevalence of Hypercortisolism in CATALYST

Hypercortisolism defined as post-DST cortisol >1.8 µg/dL with dexamethasone ≥140 ng/dL in this population, which has a high pre-test probability of hypercortisolism and excludes known causes of false-positives



252 of 1057
CATALYST participants screened have hypercortisolism

Prevalence estimate was stable after ~200 patients had been recruited

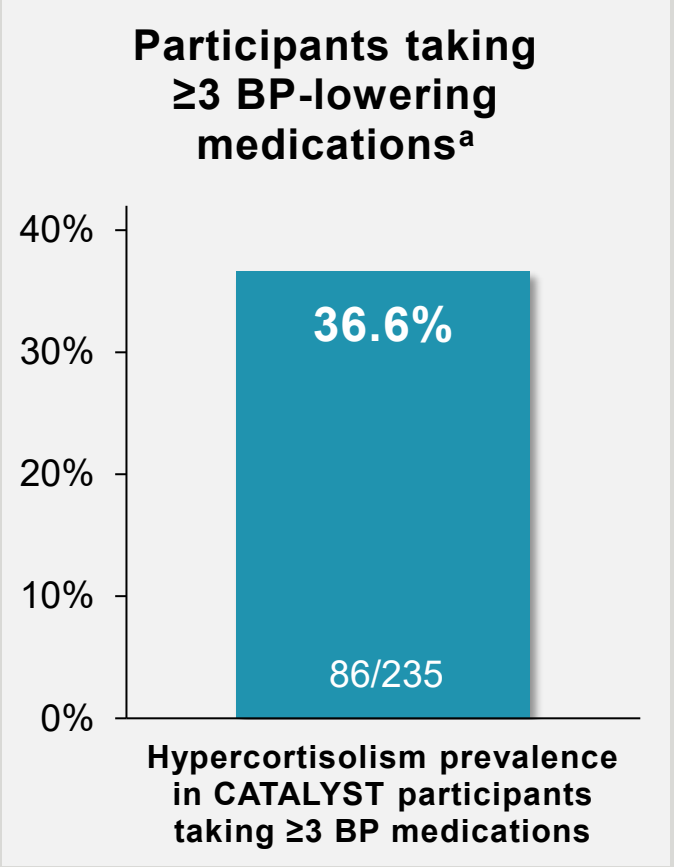
Mean (SD) post-DST cortisol: 3.5 (2.8) µg/dL
Mean (SD) post-DST dexamethasone: 412.5 (219.9) ng/dL

Buse, Kahn et al. *Diabetes Care* 2025:dc242841. DST, dexamethasone suppression test; SD, standard deviation.

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

Population of Interest: 36.6% of Those Taking ≥3 Antihypertensives Had Hypercortisolism

- **22.2%** of CATALYST participants were taking ≥3 blood pressure-lowering medications (235/1057)
  - Among those, the prevalence of hypercortisolism was **36.6%**
- The odds of having hypercortisolism were **2× as high** in those taking ≥3 blood pressure-lowering medications (OR 2.281, 95% CI 1.66, 3.127)



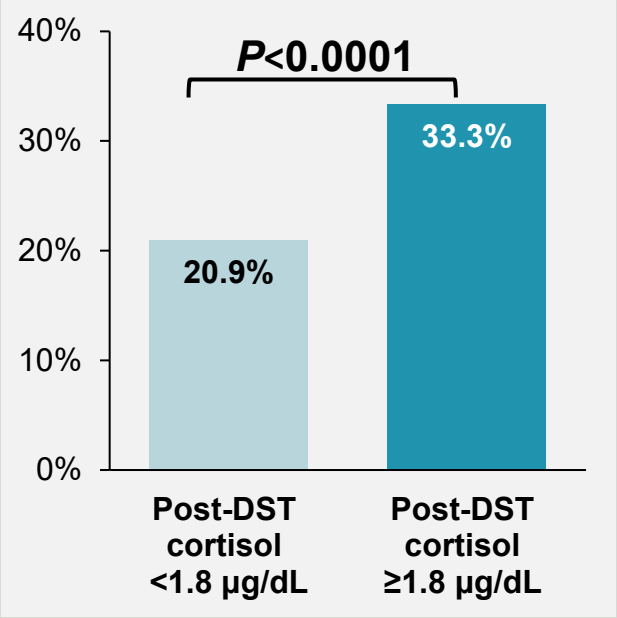
Buse, Kahn et al. *Diabetes Care* 2025:dc242841. [a]Odds ratio and 95% CI from a univariate logistic regression model for hypercortisolism vs no hypercortisolism performed separately for each variable. BP, blood pressure; CI, confidence interval; DST, dexamethasone suppression test; OR, odds ratio; T2D, type 2 diabetes.

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

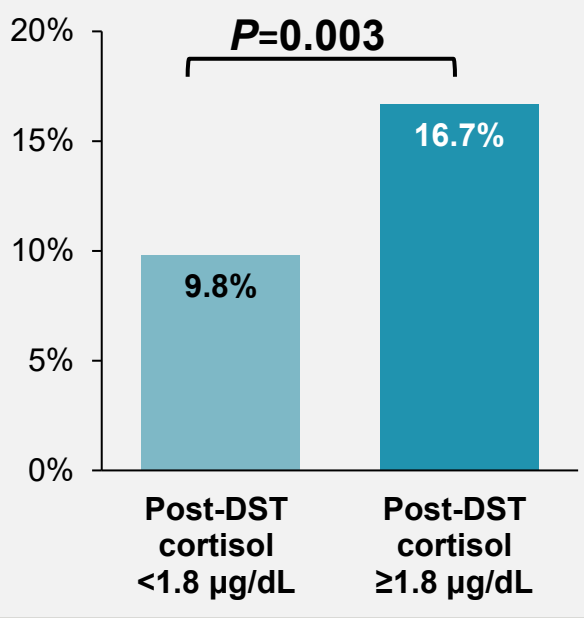
Screening Phase

Comorbidity of Interest: Participants With Hypercortisolism Had More Cardiovascular Disease

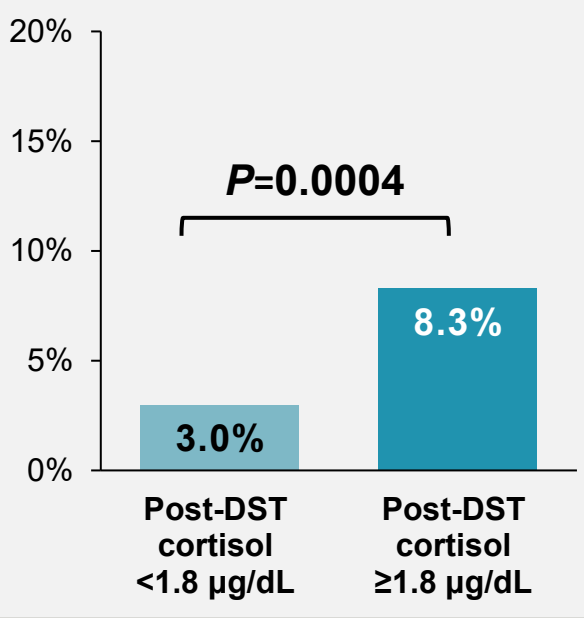
Cardiac disorders overall



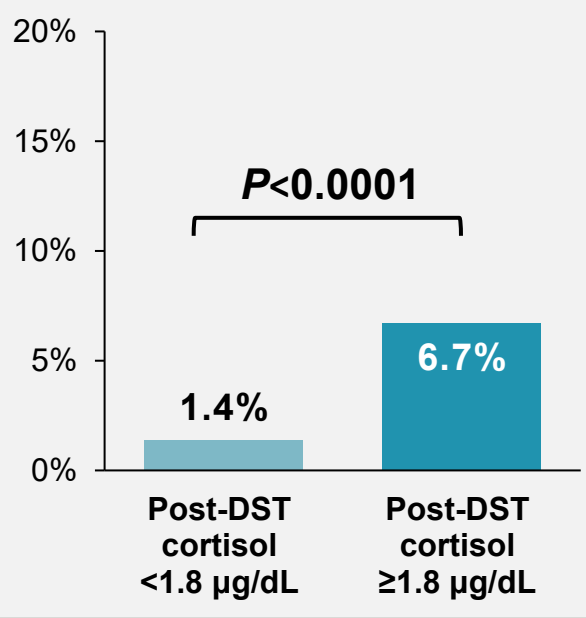
Coronary artery disease



Atrial fibrillation



Congestive cardiac failure



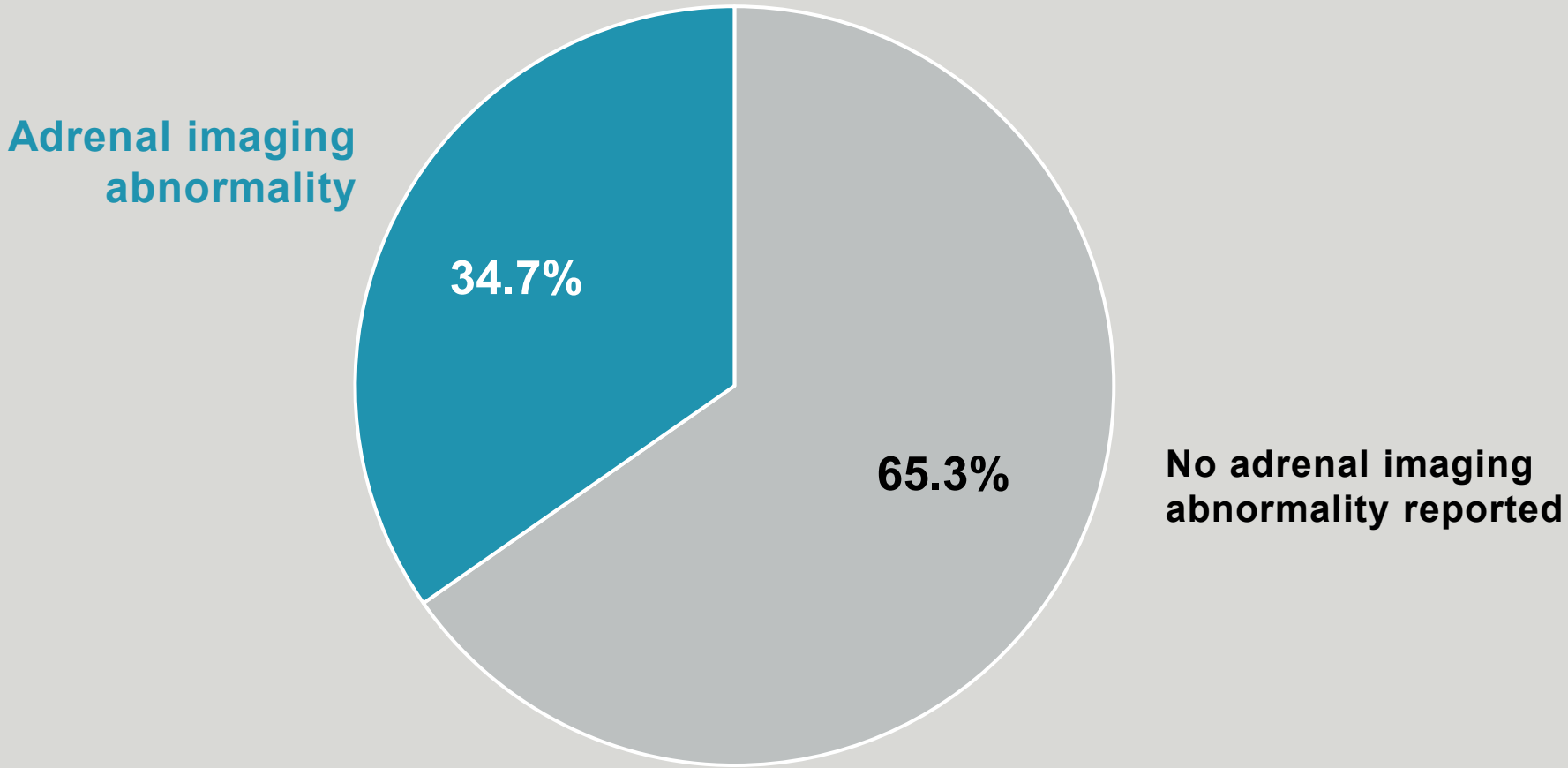
- Patients with T2D are at higher CVD risk, and this risk appears to increase further in those who also have hypercortisolism
- Consistent with the observation that CATALYST participants with hypercortisolism had a higher overall medication burden

Buse, Kahn et al. *Diabetes Care* 2025:dc242841. *P*-values from a chi-squared test. CVD, cardiovascular disease; DST, dexamethasone suppression test; T2D, type 2 diabetes.

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

Screening Phase

Adrenal Imaging Abnormality Reported in One Third of CATALYST Participants With Hypercortisolism



Buse, Kahn et al. *Diabetes Care* 2025:dc242841. Abdominal CT scan results were available in 219/252 (86.9%) participants. Reasons for not completing the CT scan were withdrawal of consent (n=13), lost to follow up (n=6), physician decision (n=2), and other (n=12).

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

Key Endpoints for Part 2: Evaluate the Safety and Efficacy of Mifepristone Treatment in These Participants

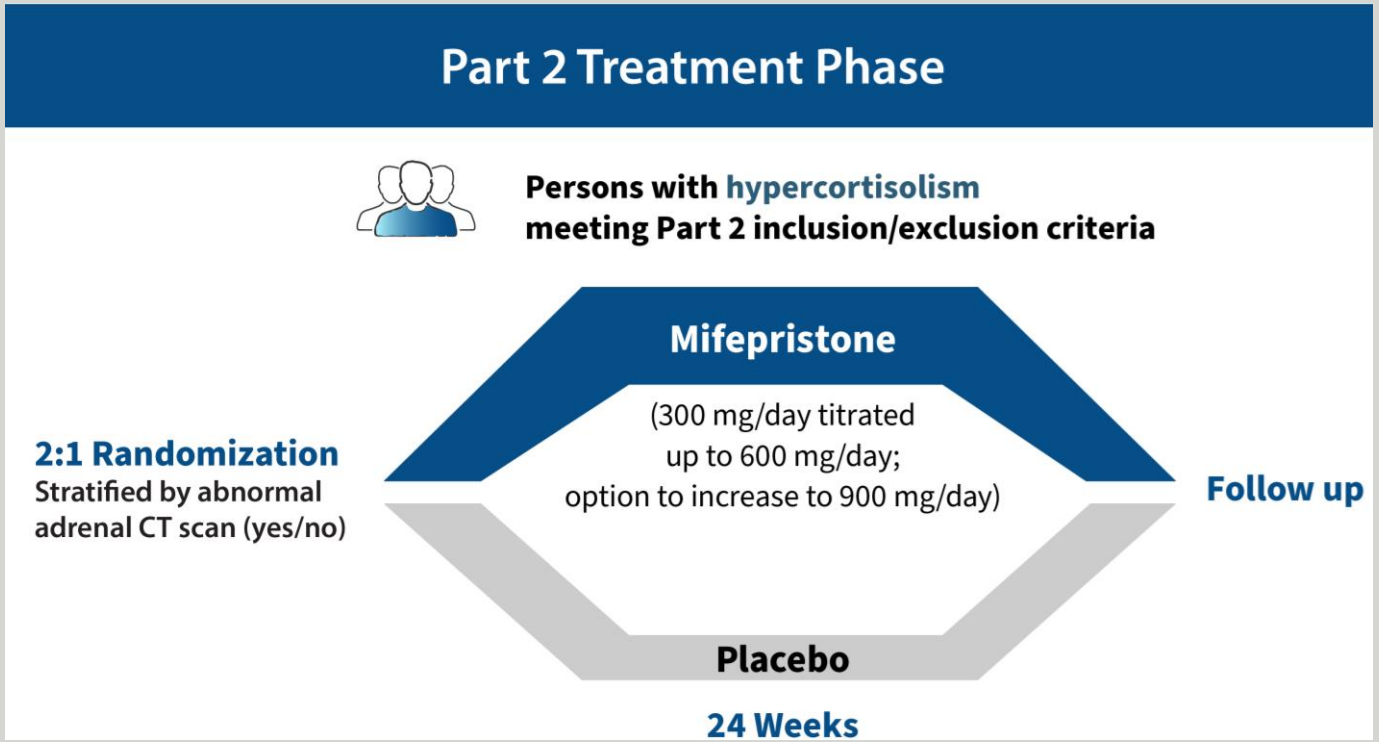
- Enrolled **136** participants

Primary Endpoint

- Change in HbA1c from baseline to week 24 for mifepristone compared to placebo

Key Secondary Endpoints

- Changes in glucose-lowering medications
- Changes in hypercortisolism-related comorbidities (eg, glycemic metrics, weight, waist circumference, BMI, BP, lipids)
- Differences between participants with and without adrenal imaging abnormalities

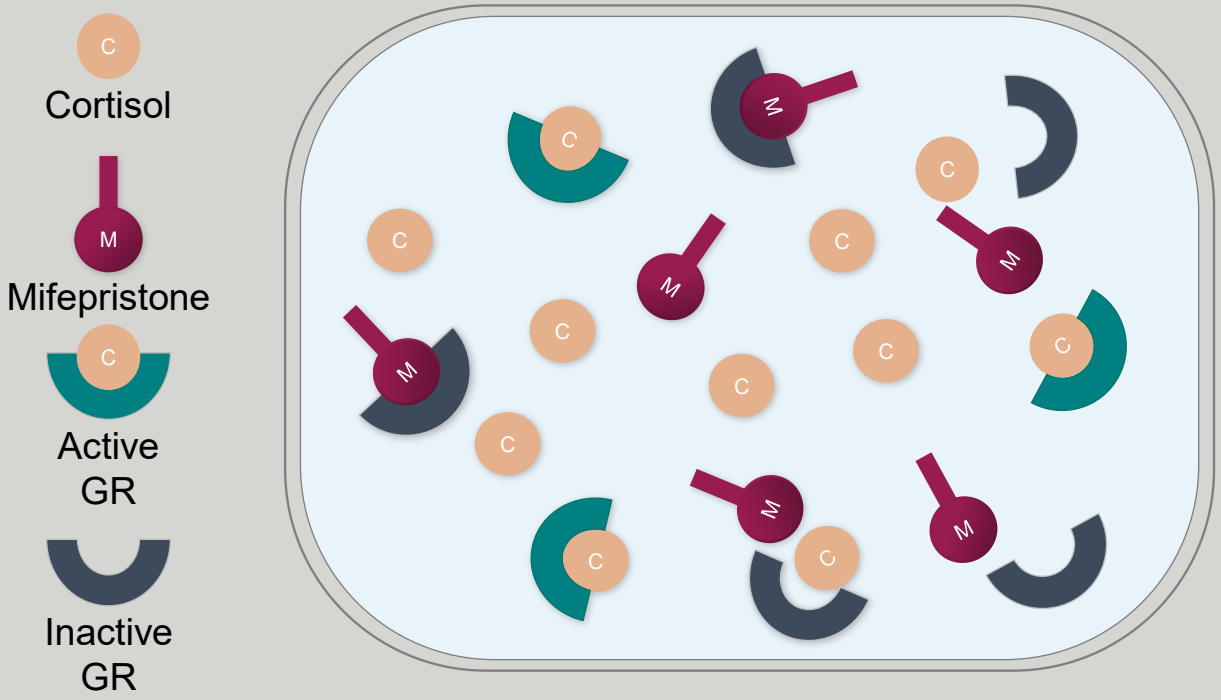


Statistical Methods:

- 90% power to detect a difference in change from baseline to week 24 in HbA1c between groups of at least 1.5% with 114 participants, based on a t-test with α=0.05
- Primary endpoint analysis applied a restricted maximum likelihood-based mixed-effect model for repeated measurements in the intent-to-treat population

BMI, body mass index; BP, blood pressure; HbA1c, hemoglobin A1c; T2D, type 2 diabetes.

What Is Mifepristone and How Does it Work?



Mifepristone Is a Competitive Glucocorticoid Receptor Antagonist

- Binds to the glucocorticoid receptor, decreasing cortisol-mediated signaling[1-3] and reducing the clinical effects of hypercortisolism[4]
- FDA approved for the treatment of hyperglycemia secondary to hypercortisolism in adult patients with endogenous Cushing syndrome who have T2D or glucose intolerance[5]

GR, glucocorticoid receptor; T2D, type 2 diabetes.

1. Bourgeois S, et al. *EMBO* J. 1984;3(4):751-755. 2. Heikinheimo O, et al. *J Steroid Biochem*. 1987;26(2):279-284. 3. Sitruk-Ware R, Spitz IM. *Contraception*. 2003;68(6):409-420.
4. Katznelson L, et al. *Clin Endocrinol (Oxf)*. 2014;80(4):562-569. 5. Korlym [prescribing information]. Redwood City, CA: Corcept Therapeutics Incorporated; September 2024.

Key Inclusion & Exclusion Criteria

Rationale for ACTH criteria: Exclude patients with high ACTH from a placebo-controlled trial

Completed the prevalence phase with hypercortisolism (post-DST cortisol >1.8 µg/dL)

Adrenal abnormality on CT scan
(nodule, enlargement, or other abnormality)

Eligible if
- 8 AM ACTH ≤15 pg/dL OR
- 15–30 pg/dL with DHEAS ≤100 µg/dL

+ other eligibility criteria met

No adrenal abnormality on CT scan

Eligible if
- 8 AM ACTH below the upper normal range

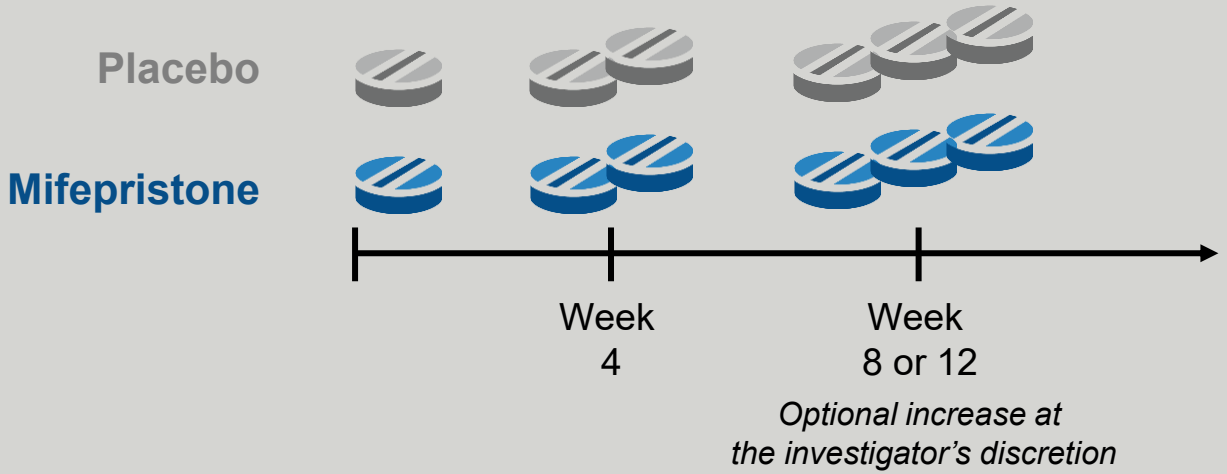
+ other eligibility criteria met

1. Unable to correct BP to <160/100 mmHg
2. Unable to correct potassium to ≥4.0 mEq/L
3. Unable to control hypo- or hyperthyroidism
4. Taking or at risk for taking systemic glucocorticoids due to an underlying condition (eg, asthma)
5. Liver transaminases >3× ULN or total bilirubin >1.5× ULN
6. eGFR <30 mL/min/1.73 m^2
7. Taking drugs metabolized by CYP3A or CYP3A substrates with narrow therapeutic ranges
8. History of unexplained vaginal bleeding, endometrial hyperplasia, or endometrial carcinoma

ACTH, adrenocorticotropic hormone; BP, blood pressure; CT, computed tomography; DHEAS, dehydroepiandrosterone sulfate; DST, dexamethasone suppression test; eGFR, estimated glomerular filtration rate; ULN, upper limit of normal.

Study Medication & Management

- **Mifepristone** administered as 300 mg tablet(s), identical placebo
  - Tablets taken once daily at approximately the same time with food
- **Dosing schedule was individualized** to allow for lower doses, slower titration, dose interruption, and dose reduction / re-escalation for safety and tolerability
- **Biweekly visits** were scheduled to monitor glucose, potassium, blood pressure, and symptoms of glucocorticoid withdrawal

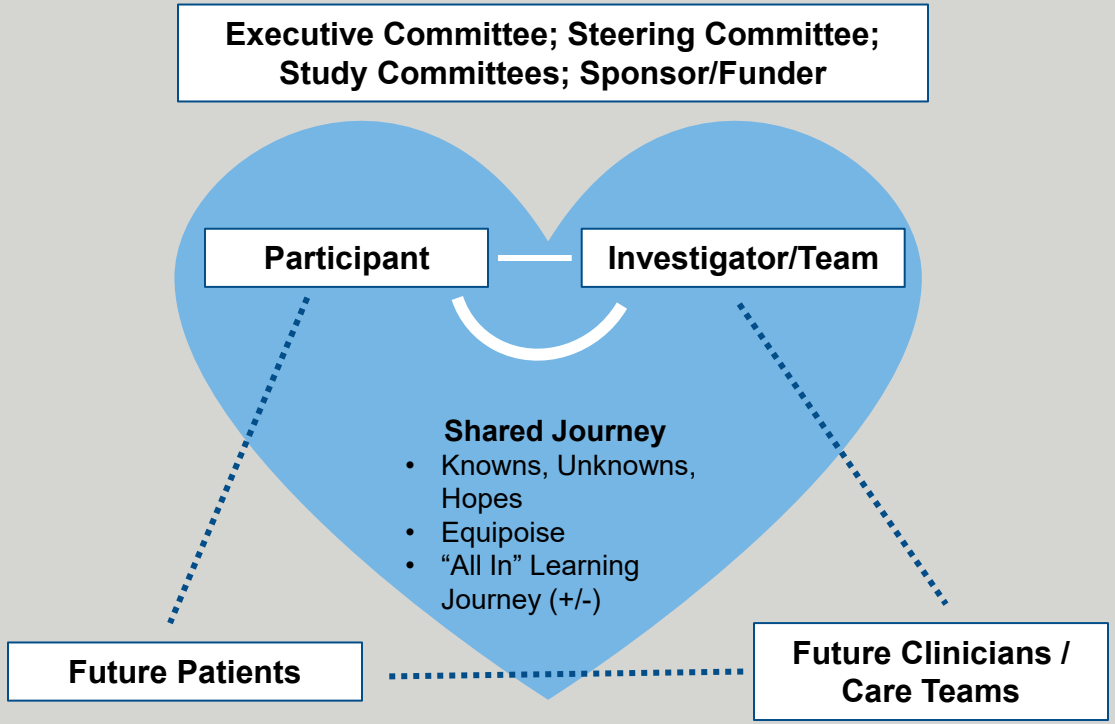


Summary: Design of the CATALYST Trial & Prevalence Results

CATALYST was the largest, prospective study to date assessing the prevalence and the impact of pharmacological treatment of hypercortisolism in patients with difficult-to-control T2D

Prevalence phase results

- **Hypercortisolism prevalence of 23.8%** in the overall study population (n=1057)
- **Hypercortisolism prevalence of 36.6%** among participants **who took ≥3 BP-lowering medications** in addition to their glucose-lowering medications
- **In one third of participants** with hypercortisolism, a standard abdominal CT scan revealed an adrenal abnormality



Aroda VR. *Academic Medicine* 2022; 97(11):1672. BP, blood pressure; CT, computed tomography.