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

A Phase 4 Study of Hypercortisolism in Patients with Difficult-to-Control Type 2 Diabetes Despite Receiving Standard-of-Care Therapies, Assessing Prevalence and Treatment with Mifepristone

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Summary & Conclusions

- Primary hypercortisolism is under-recognized.
- Even in the absence of classic Cushingoid features, all degrees of hypercortisolism are associated with significant morbidity and mortality.
- Primary hypercortisolism has been shown to be particularly common in persons with difficult-to-control T2D, but reliable prevalence estimates are currently lacking.
- CATALYST is the first prospective study to assess the prevalence of primary hypercortisolism and the benefit of cortisol-directed medical treatment of primary hypercortisolism in persons with difficult-to-control T2D.
  - Hypercortisolism prevalence is being assessed based on risk factors and screening with DST; ACTH, DHEAS, and adrenal CT scan are being used for further evaluation.
  - Medical therapy with the glucocorticoid receptor antagonist Korlym® (mifepristone) is being evaluated in this population in a prospective, placebo-controlled, randomized design.
- CATALYST is currently enrolling.

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

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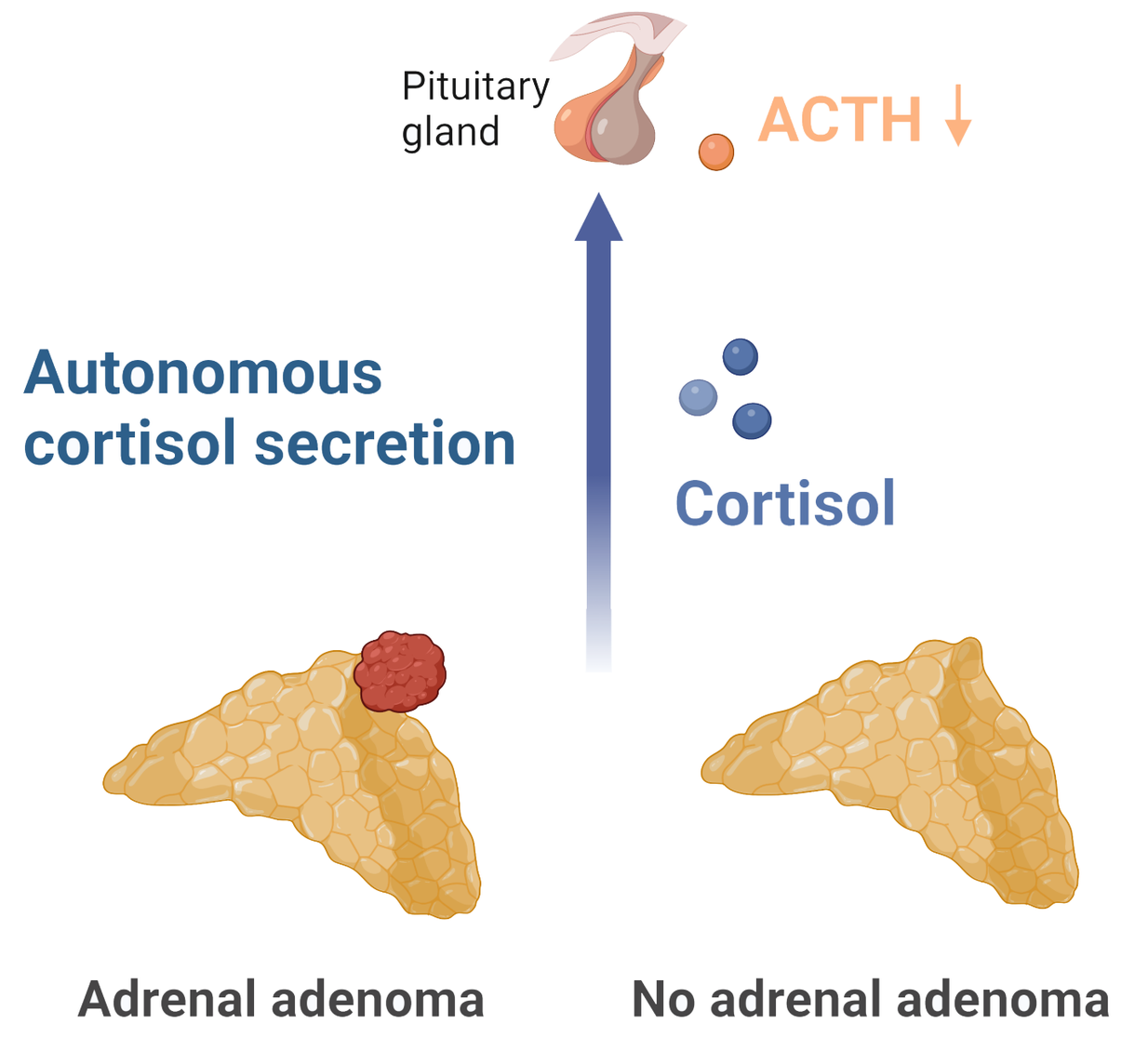
Background

Primary Hypercortisolism: An Under-recognized, Serious Disease

- Primary hypercortisolism is caused by ACTH-independent, autonomous cortisol secretion by the adrenal glands.
- The understanding of primary hypercortisolism and its clinical significance have evolved significantly in recent years.
  - Primary hypercortisolism may be more common than generally appreciated.[1]
  - Even in the absence of the classical physical features of Cushing syndrome[2], persons with all degrees of primary hypercortisolism have an increased risk of cardiovascular (CV) events, comorbidities, and mortality, even if comorbidities are managed.[3-5]
  - Difficult-to-control T2D, treatment-resistant hypertension, and/or osteoporosis may be clinical manifestations of primary hypercortisolism.[6]



Prevalence of Primary Hypercortisolism in Persons with T2D

- Prevalence estimates vary widely.
- Prevalence may be especially high in those with difficult-to-control and/or advanced T2D (multiple therapies and comorbidities).[6-12]
- Current prevalence estimates are limited by small sample sizes, different definitions of hypercortisolism, varying degrees of severity of T2D and comorbidities, retrospective designs, ascertainment bias, and incomplete data.

HYPERCORTISOLISM PREVALENCE
~3.5× higher
in persons with advanced vs. less severe T2D[6,13]

Screening for Primary Hypercortisolism

- Recommended screening test: 1-mg overnight DST
  - Post-DST serum cortisol >1.8 µg/dL indicates autonomous cortisol secretion[14], along with adequate dexamethasone level and suppressed early-morning ACTH.
  - Adrenal CT can determine the presence or absence of adrenal adenoma(s) in persons with abnormal DST and ACTH.
- 24-hour urinary free cortisol is frequently normal in persons with adrenal autonomous cortisol secretion.[1]
- Late-night salivary cortisol may have low sensitivity for predicting adrenal autonomous cortisol secretion.[15]

Premise

- There is a significant need to better understand the prevalence of primary hypercortisolism in persons with difficult-to-control T2D and whether medical treatment of hypercortisolism may result in better control of hyperglycemia and other hypercortisolism-associated comorbidities.
- CATALYST is the first prospective study designed to answer these questions.
- Korlym® (mifepristone), a competitive glucocorticoid receptor antagonist indicated to control hyperglycemia secondary to hypercortisolism in adults with endogenous Cushing syndrome who have T2D or glucose intolerance and have failed surgery or are not candidates for surgery, is used in the treatment phase of the study.

Abstract

The prevalence of hypercortisolism in persons with difficult-to-control type 2 diabetes (T2D) may be higher than currently appreciated, particularly in persons who require a greater number of antihyperglycemic agents and/or have more comorbidities. To better understand the prevalence and whether treatment of hypercortisolism may result in better control of diabetes and other hypercortisolism-associated comorbidities, we have designed CATALYST, a prospective phase 4 study in adults with difficult-to-control T2D (HbA1c 7.5–11.5%) despite receiving multiple antihyperglycemic agents. CATALYST is being conducted at about 30 sites in the United States. In Part 1, about 1000 persons with difficult-to-control T2D will be screened with a 1-mg dexamethasone suppression test (cutoff: serum cortisol >1.8 µg/dL; dexamethasone ≥140 ng/dL). Patients with ACTH-dependent hypercortisolism will be referred out of the study. The primary study endpoint—the prevalence of ACTH-independent hypercortisolism—will be evaluated in Part 1. Patients with ACTH-independent hypercortisolism may advance to Part 2, a prospective, 2:1 randomized, double-blind, placebo-controlled trial to evaluate the efficacy and safety of treatment with the competitive glucocorticoid receptor antagonist mifepristone. Patients will be randomized (stratified by the presence/absence of adrenal adenomas on CT) and receive treatment for 24 weeks. The mifepristone dose will be 300 mg QD for 4 weeks, then increased to 600 mg QD for 20 weeks based on glycemic efficacy and tolerability (option to increase to mifepristone 900 mg). Secondary endpoints include changes in HbA1c from baseline to 24 weeks and changes in hypercortisolism-related comorbidities (e.g., blood pressure, weight, waist circumference, quality of life).

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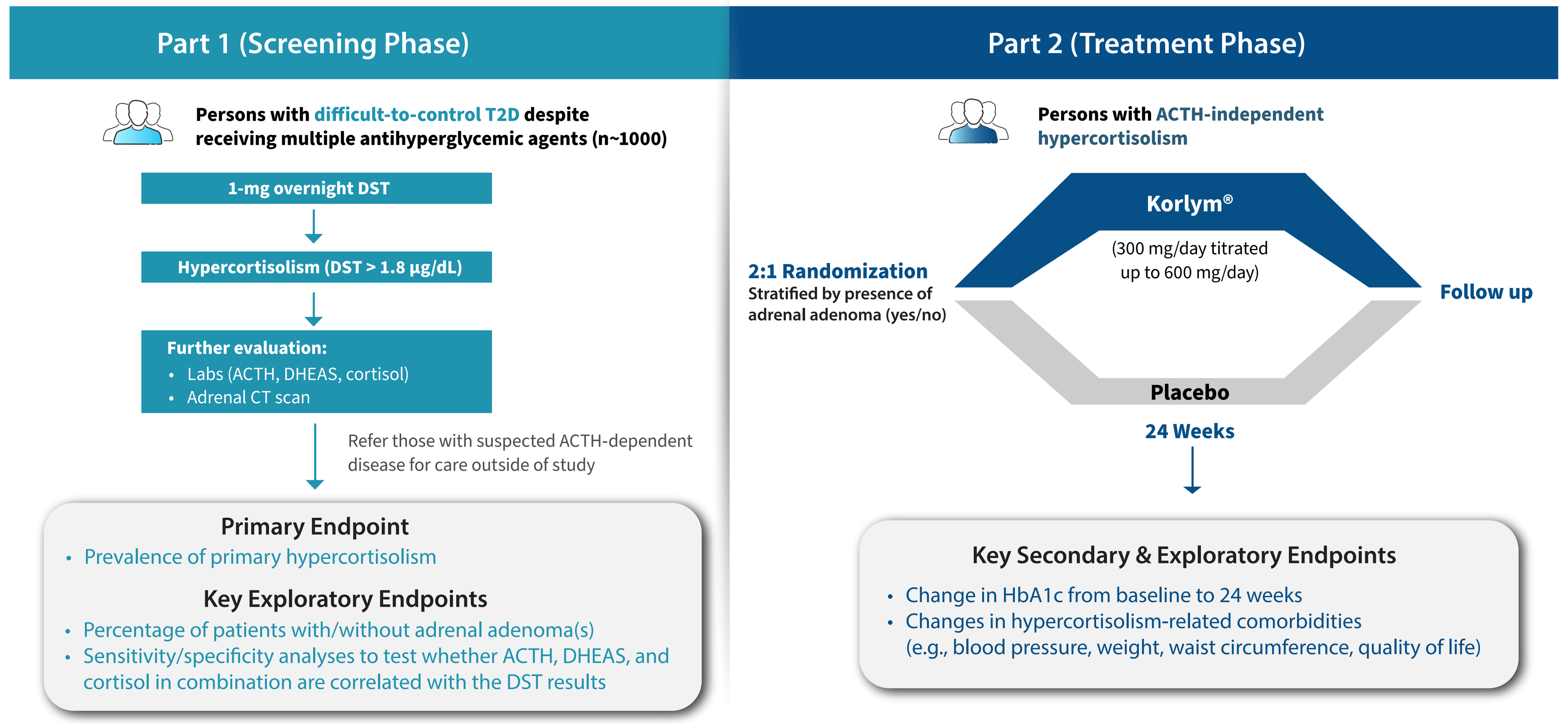
CATALYST Study Design

- A unique, 2-part phase 4 study to be conducted at approximately 30 sites in the United States (NCT05772169)



Part 1

- To assess the **prevalence of hypercortisolism** in persons with difficult-to-control T2D despite receiving multiple anti-hyperglycemic agents
  - Screening: 1-mg overnight DST with cortisol >1.8 µg/dL and dexamethasone ≥140 ng/dL
  - Further characterization with ACTH, DHEAS, cortisol, and adrenal CT
  - Those with ACTH-dependent disease will be referred for care outside of the study.
  - Those with surgically amenable disease will be informed of this treatment option.

Part 2

- To assess the tolerability, safety, and efficacy of treatment with the competitive glucocorticoid receptor antagonist Korlym (mifepristone) in persons with T2D and hypercortisolism identified in Part 1
  - Study design: Prospective, randomized, double-blind, placebo-controlled trial
  - Stratification: Presence/absence of adrenal adenoma(s) (based on non-contrast adrenal CT)
  - Study drug initiated at 1 tablet (300 mg) per day and titrated to 2 tablets (600 mg) per day at week 4. Dose titration is individualized.
  - Study drug may be titrated to 3 tablets (900 mg) per day.

Key Inclusion and Exclusion Criteria

	Key Inclusion	Key Exclusion
Part 1	• Adults (18-80 years old) with T2D • HbA1c ≥7.5% and ≤11.5%, AND taking ○ ≥3 anti-hyperglycemic drugs OR ○ insulin and other anti-hyperglycemic drug(s) OR ○ ≥2 anti-hyperglycemic drugs AND – presence of ≥1 micro-vascular or macro-vascular complication AND/OR – concomitant hypertension requiring ≥2 anti-hypertension medications	• Type 1 diabetes mellitus • Prior diagnosis of Cushing syndrome or past, current, or planned use of Cushing syndrome treatments • Night shift worker, alcohol excess, severe untreated sleep apnea • Severe medical, surgical, or psychiatric stress • On oral contraceptive pills and unable to hold for 3–4 weeks pre-DST • Exposure to systemic glucocorticoid medications (excluding inhalers or topical) within 3 months of screening
Part 2	• Completed Part 1 with DST >1.8 µg/dL and dexamethasone level ≥140 ng/dL • No increase or initiation of new anti-hyperglycemic medications within 4 weeks prior to first dose	• Korlym use contraindicated • Refractory hypokalemia • Poorly controlled hypothyroidism or hyperthyroidism • Severe, poorly controlled hypertension (mean systolic BP >160 mm Hg or mean diastolic BP >100 mm Hg)