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Crenessity™ (crinecerfont) Capsules 50mg, 100mg

PUBLICATION ON THE CAHtalyst™ TRIAL:

Phase 3 Trial of Crinecerfont in Adult Congenital Adrenal Hyperplasia

Auchus RJ, Hamidi O, Pivonello R, et al. *N Engl J Med*. 2024;391(6):504-514.

INDICATION

CRENESSITY (crinecerfont) is indicated as adjunctive treatment to glucocorticoid replacement to control androgens in adults and pediatric patients 4 years of age and older with classic congenital adrenal hyperplasia (CAH).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

CRENESSITY is contraindicated in patients with hypersensitivity to crinecerfont or any excipients of CRENESSITY.

Please see Important Safety Information throughout and accompanying CRENESSITY full Prescribing Information.

A Phase 3 Trial of CRENESSITY in Adult Patients With Classic Congenital Adrenal Hyperplasia

Objective

This phase 3, multinational, randomized trial was conducted to evaluate the efficacy and safety of CRENESSITY to improve androgen control and allow for glucocorticoid (GC) dose reduction to a physiologic range while androstenedione (A4) levels were maintained or improved in adult patients with classic congenital adrenal hyperplasia (CAH).[1]

Methods

Study Population

Of the 300 adults screened for study entry, 182 met the eligibility criteria and were randomized (2:1) to the CRENESSITY or placebo group.

KEY INCLUSION CRITERIA

- Medically confirmed diagnosis of classic CAH
- Must be on a supraphysiologic dose of GC (>13 mg/m^2/day in hydrocortisone equivalent adjusted for body surface area)[a]
- Stable GC dose for at least 1 month prior to screening

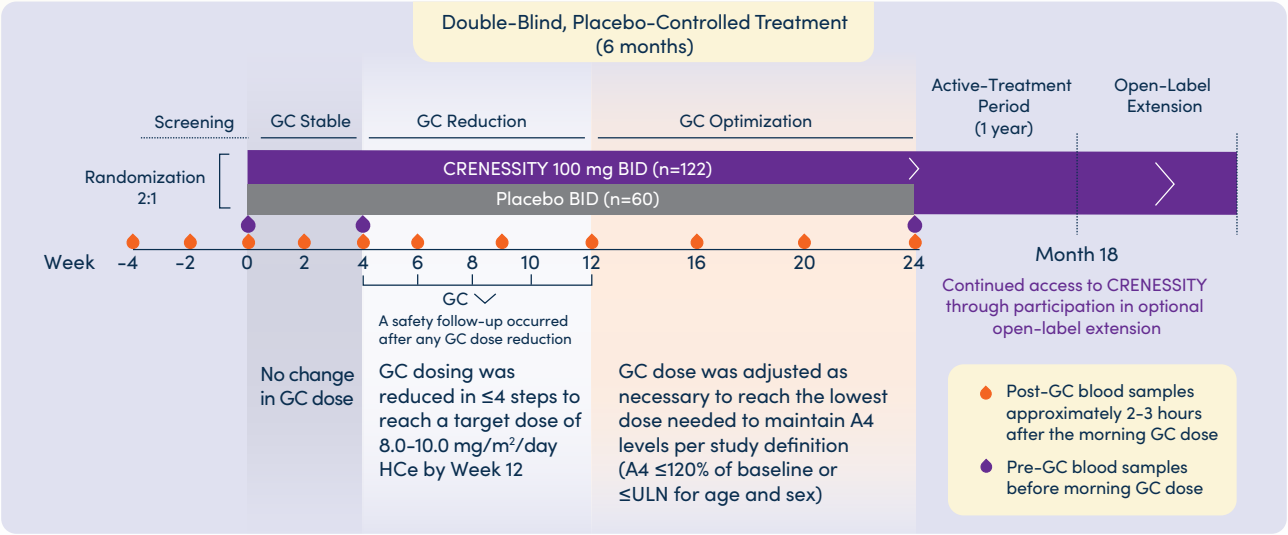
KEY EXCLUSION CRITERIA

- Any other non-CAH condition that required long-term GC treatment
- Evidence of GC overtreatment (as measured by progesterone or A4 level below normal)
- At risk for developing adrenal crisis (per investigator judgment)

[a]Supraphysiologic dose was defined by clinical study design.
A4=androstenedione; CAH=congenital adrenal hyperplasia; GC=glucocorticoid.

Study Design

The CAHtalyst™ adult trial was a 24-week, randomized, double-blind, placebo-controlled period followed by a 12-month active-treatment period. An optional open-label extension is ongoing.



A4=androstenedione; BID=twice daily; GC=glucocorticoid; HCe=hydrocortisone equivalents; ULN=upper limit of normal.

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions. A hypersensitivity reaction, including throat tightness, angioedema, and generalized rash, occurred in a subject after 3 days of treatment with CRENESSITY. If a clinically significant hypersensitivity reaction occurs, initiate appropriate therapy and discontinue CRENESSITY.

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HYPOTHESIS 1

CRENESSITY can reduce A4 while holding GC dose stable

Androgen reduction was evaluated at Week 4.

- Key secondary endpoint: A4 serum levels (change from baseline)
- Secondary endpoint: 17-OHP serum levels (change from baseline)

HYPOTHESIS 2

CRENESSITY allows for GC reduction while maintaining A4 levels[a]

GC dose reduction with androgen control was evaluated at Week 24.

- Primary endpoint: GC daily dose (percent change from baseline)[b]
- Secondary endpoint: GC daily dose (percent of patients with reduction to a physiologic range)

[a]A4 maintenance was defined as ≤120% of baseline or ≤ULN according to sex and age.
[b]Decreases in GC dose were set to 0 in participants who did not maintain androgen levels.
17-OHP=17-hydroxyprogesterone; A4=androstenedione; GC=glucocorticoid; ULN=upper limit of normal.

Results

Efficacy Endpoints[1,2]

Primary Efficacy Endpoint	Treatment Group	Mean (SD) Baseline	LS Mean (SEM) Percent Change From Baseline	Placebo-Subtracted LS Mean Difference (95% CI)
Percent Change From Baseline in GC Daily Dose While Maintaining A4 Control at Week 24 in Adult Patients With CAH				
GC Daily Dose ($mg/m^2/day$)[a]	CRENESSITY (n=122)	17.5 (4.5)	-27.3% (2.4)	-17.0 (-23.8, -10.2) *P*<0.001
	Placebo (n=60)	17.9 (5.5)	-10.3% (3.2)	

[a]In hydrocortisone equivalents (4x equivalency factor for (methyl)predniso(lo)ne, 60x for dexamethasone) adjusted for body surface area.
A4=androstenedione; CAH=congenital adrenal hyperplasia; CI=confidence interval; GC=glucocorticoid; LS mean=least-squares mean; SD=standard deviation; SEM=standard error of the mean.

Key Secondary Efficacy Endpoint	Treatment Group	Mean (SD) Baseline	LS Mean (SEM) Change From Baseline	Placebo-Subtracted LS Mean Difference (95% CI)
Change From Baseline in Serum A4 at Week 4[a] in Adult Patients With CAH				
Serum A4 (ng/dL)[b]	CRENESSITY (n=122)	635 (796)	-299 (37.7)	-345 (-457, -232) *P*<0.001
	Placebo (n=60)	590 (572)	45.5 (51.0)	

[a]End of GC stable period.
[b]Obtained prior to the morning GC dose.
A4=androstenedione; CAH=congenital adrenal hyperplasia; CI=confidence interval; GC=glucocorticoid; LS mean=least-squares mean; SD=standard deviation; SEM=standard error of the mean.

Key Secondary Efficacy Endpoint

At Week 24, there was a statistically significantly greater percentage of patients achieving a reduction to a physiologic GC daily dose (≤11 mg/m^2/day hydrocortisone equivalents) while A4 was controlled (≤120% of baseline or less than or equal to the upper limit of normal) with CRENESSITY compared to placebo (63% vs 18%, *P*<0.001).

IMPORTANT SAFETY INFORMATION (continued)

WARNINGS AND PRECAUTIONS

Risk of Acute Adrenal Insufficiency or Adrenal Crisis with Inadequate Concomitant Glucocorticoid Therapy. Acute adrenal insufficiency or adrenal crisis, which is potentially life-threatening, can occur in patients with underlying adrenal insufficiency who are on inadequate daily glucocorticoid doses, especially in situations associated with increased cortisol need, such as acute intercurrent illness, serious trauma, or surgical procedures. Continue glucocorticoids upon initiation of and during treatment with CRENESSITY. Do not reduce the glucocorticoid dose below the dose required for cortisol replacement. Patients should continue to use stress dosing of glucocorticoids in cases of increased cortisol need.

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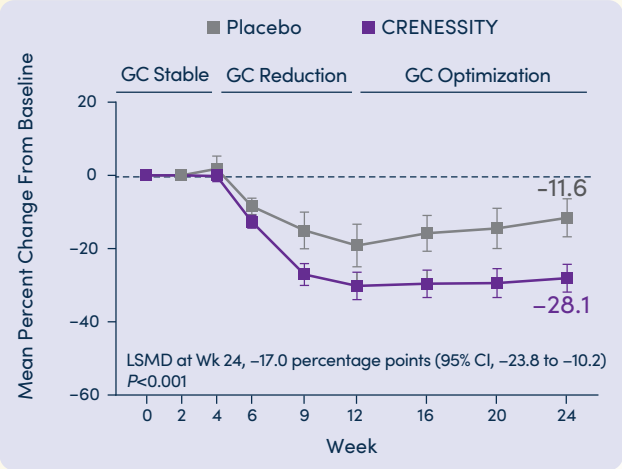
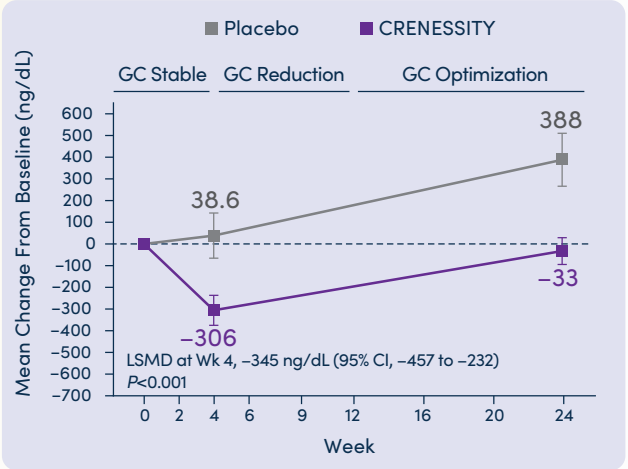
Percent Change From Baseline in GC Dose With Maintenance of A4 Control



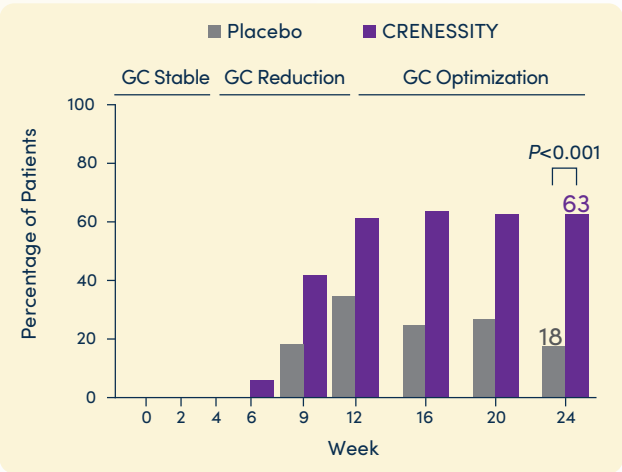
CRENESSITY significantly reduced GC total daily dose while maintaining A4 control (≤120% of baseline A4 measurements or within the ULN) at Week 24 compared with placebo (LSM percent change from baseline of -27.3% vs -10.3%; LSMD of -17.0 percentage points; *P*<0.001).

Change From Baseline in A4



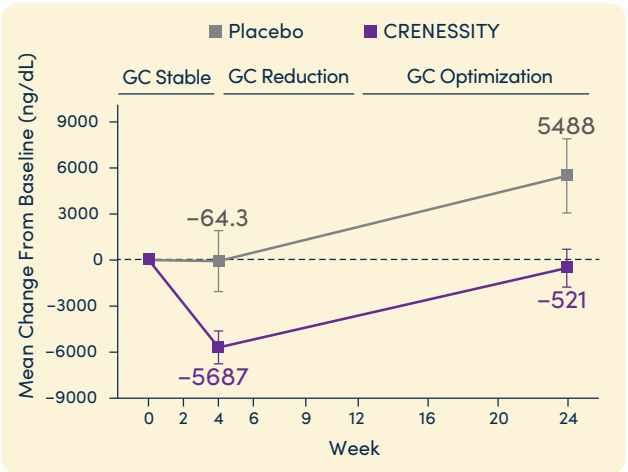
During the initial 4-week stable period, the LSM level of A4 decreased with CRENESSITY (−299 ng/dL) but increased with placebo (45.5 ng/dL), for an LSMD of −345 ng/dL; *P*<0.001. At Week 24, after the reduction in the GC dose and the optimization period, the mean A4 level remained below baseline with CRENESSITY (−33.0 ng/dL) but increased to above baseline with placebo (388 ng/dL).

Physiologic GC Dose With Maintenance of A4 Control



The percentage of participants who had a reduction to a physiologic GC dose (≤11 mg/m^2/day) while maintaining baseline A4 levels was significantly greater in the CRENESSITY group (63%) than in the placebo group at Week 24 (18%); *P*<0.001.

Change From Baseline in 17-OHP



17-OHP levels were reduced substantially from baseline to Week 4 with CRENESSITY but changed minimally with placebo.

17-OHP=17-hydroxyprogesterone; A4=androstenedione; GC=glucocorticoid; LSM=least-squares mean; LSMD=least-squares mean difference; ULN=upper limit of normal.

IMPORTANT SAFETY INFORMATION (continued)

ADVERSE REACTIONS

In adult patients, the most common adverse reactions (at least 4% for CRENESSITY and greater than placebo) are fatigue, headache, dizziness, arthralgia, back pain, decreased appetite, and myalgia.

In pediatric patients, the most common adverse reactions (at least 4% for CRENESSITY and greater than placebo) are headache, abdominal pain, fatigue, nasal congestion, and epistaxis.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit MedWatch at www.fda.gov/medwatch or call 1-800-FDA-1088.

Please see Important Safety Information throughout and accompanying CRENESSITY full Prescribing Information.

Safety

In this trial, CRENESSITY had a demonstrated safety profile in a clinically complex patient population. The table below summarizes commonly observed adverse reactions in the clinical trial that occurred over 24 weeks (incidence ≥4% with CRENESSITY and more frequent than with placebo).[2]

Commonly Observed Adverse Reactions in Adult Patients

Adverse Reaction	Placebo (n=59)	CRENESSITY (n=122)
Fatigue	15%	25%
Headache	15%	16%
Dizziness	3%	8%
Arthralgia	0%	7%
Back pain	3%	6%
Decreased appetite	2%	4%
Myalgia	3%	4%

Patients taking CRENESSITY had no treatment-related serious adverse events. Most adverse events, including fatigue, were mild to moderate in intensity and resolved spontaneously. No safety concerns related to vital signs, clinical laboratory tests, electrocardiographic findings, or neuropsychiatric assessments were observed in phase 3 trial participants taking CRENESSITY.[1,2]

In CAHtalyst Adult, 1.6% of patients taking CRENESSITY experienced adrenal crisis. No patients on placebo experienced adrenal crisis, however, 1.7% experienced adrenal insufficiency. Please talk with your patients about the importance of continuing GC dosing while on CRENESSITY. Acute adrenal crisis can occur in patients with underlying adrenal insufficiency, especially in situations associated with increased cortisol need, such as acute illness, serious trauma, or surgical procedures.[2]

CRENESSITY had a demonstrated tolerability profile in the patient population. A total of 96% of adults treated with CRENESSITY completed the 24-week, phase 3 trial (N=122). Four patients experienced adverse events that ultimately led to drug and trial discontinuation. These were dyspepsia, nausea, and vomiting in 1 patient; gastric ulcer in 1 patient; apathy and restlessness in 1 patient; and rash in 1 patient. These patients were first identified during the randomized period, and only the patient with the gastric ulcer discontinued the study during that phase.[1]

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Summary of Findings

CRENESSITY improves or maintains androgens and allows for a meaningful reduction in GC doses in adults with CAH.

- Treatment with CRENESSITY resulted in a −27.3% reduction in the mean daily GC dose at Week 24 compared with a −10.3% reduction in the placebo group ($P<0.001$)
- 63% of patients treated with CRENESSITY achieved a physiologic GC dose while maintaining A4 control vs 18% in the placebo group ($P<0.001$)
- At Week 4, A4 levels decreased by −299 ng/dL with CRENESSITY, whereas they increased by 45.5 ng/dL in the placebo group ($P<0.001$)

In patients taking CRENESSITY, the most common adverse events included fatigue (25%), headache (16%), dizziness (8%), and arthralgia (7%).

- CRENESSITY has a demonstrated safety and tolerability profile in a clinically complex patient population
- The frequency of adverse events was similar in both groups, with 83% of participants in the CRENESSITY group and 81% of participants in the placebo group reporting adverse events, which were primarily mild to moderate in severity
- Fatigue was more common in the CRENESSITY group (25% vs 15% in placebo); most adverse events resolved spontaneously
- There were no deaths reported during the trial, and no significant safety issues were found related to vital signs, laboratory tests, or psychiatric assessments

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References

1. Auchus RJ, Hamidi O, Pivonello R, et al. Phase 3 trial of CRENESSITY in adult congenital adrenal hyperplasia. *N Engl J Med*. 2024;391(6):504-514. doi:10.1056/NEJMoa2404656
2. CRENESSITY [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.

NEUROCRINE® BIOSCIENCES

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