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Crenessity™ (crinecerfont)
Capsules 50mg, 100mg

PUBLICATION ON THE CAHtalyst™ TRIAL:

Phase 3 Trial of Crinecerfont in Pediatric Congenital Adrenal Hyperplasia

Sarafoglou K, Kim MS, Lodish M, et al. *N Engl J Med.* 2024;391(6):493-503.

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 Pediatric Patients With Classic Congenital Adrenal Hyperplasia

Objective

This phase 3, multinational, randomized trial was conducted to evaluate the efficacy and safety of CRENESSITY in reducing androstenedione (A4) levels and in lowering glucocorticoid (GC) daily dose while maintaining adrenal androgen concentrations in pediatric patients with classic congenital adrenal hyperplasia (CAH).[1]

Methods

Study Population

Of the 174 children and adolescents screened, 103 met the eligibility criteria and were randomly assigned, in a 2:1 ratio, to receive CRENESSITY or placebo.

KEY INCLUSION CRITERIA

- Supraphysiologic dose of GC (>12 mg/m^2/day in hydrocortisone dose equivalents adjusted for body surface area)[a] for ≥1 month prior to screening
- A4 levels greater than the midpoint of the reference range[b]
- 17-OHP levels of more than 2 times the ULN range[c]

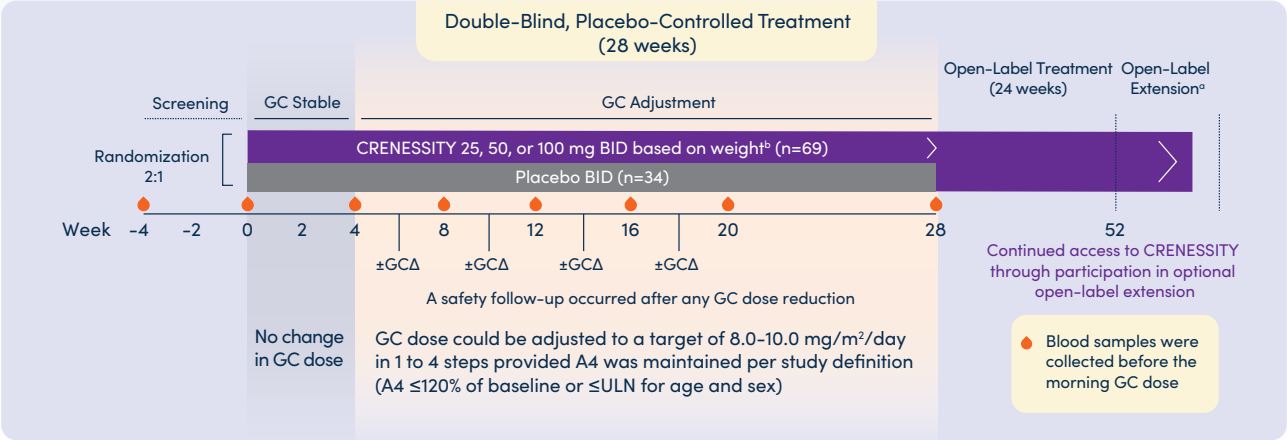
KEY EXCLUSION CRITERIA

- Known or suspected diagnosis of another form of classic CAH
- Presence of clinically significant medical condition or chronic disease that would interfere with or confound study (per investigator judgment)
- History of conditions other than CAH requiring chronic daily GC therapy (per investigator judgment)

[a]Supraphysiologic dose was defined by clinical study design.
[b]For patients who were unable to maintain A4 control, the percent change from baseline for daily GC dose was recorded as 0.
[c]Based on Tanner stage.
17-OHP=17-hydroxyprogesterone; A4=androstenedione; CAH=congenital adrenal hyperplasia; GC=glucocorticoid; ULN=upper limit of normal.

Study Design

The CAHtalyst™ pediatric trial was a 28-week, randomized, double-blind, placebo-controlled period followed by a 24-week open-label period. An optional open-label extension is ongoing.



[a]Duration of participation in the study is approximately 14 months for the core study and will be a variable amount of time per participant for the open-label extension.
[b]25 mg for participants with a body weight of 10 to <20 kg, 50 mg for those with a body weight of 20 to <55 kg, or 100 mg for those with a body weight of ≥55 kg.
A4=androstenedione; BID=twice daily; GC=glucocorticoid; 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.

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

HYPOTHESIS 1

CRENESSITY can reduce A4 while holding GC dose stable

Androgen reduction was evaluated at Week 4 when GC dose was stable.

- Primary endpoint: A4 serum levels (change from baseline)
- Key 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 maintenance was evaluated at Week 28.

- Key secondary endpoint: GC daily dose (percent change from baseline)[b]
- Secondary endpoint: GC daily dose (percentage of patients with reduction to a physiologic range while A4 was controlled)

[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) Change From Baseline	Placebo-Subtracted LS Mean Difference (95% CI)
Change From Baseline in Serum A4 at Week 4[a] in Pediatric Patients With CAH				
Serum A4 (ng/dL)[b]	CRENESSITY (n=69)	405 (464)	-197 (39)	-268 (-403, -132) *P*<0.001
	Placebo (n=34)	483 (456)	71 (56)	

[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	Treatment Group	Mean (SD) Baseline	LS Mean (SEM) Change From Baseline	Placebo-Subtracted LS Mean Difference (95% CI)
Change From Baseline in Serum 17-OHP at Week 4[a] in Pediatric Patients With CAH				
Serum 17-OHP (ng/dL)[b]	CRENESSITY (n=69)	8513 (7431)	-5865 (572)	-6421 (-8387, -4454) *P*<0.001
	Placebo (n=34)	9026 (5563)	556 (818)	

[a]End of GC stable period.
[b]Obtained prior to the morning GC dose.
17-OHP=17-hydroxyprogesterone; 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) 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 28 in Pediatric Patients With CAH				
GC Daily Dose[a] (mg/m^2/day)	CRENESSITY (n=69)	16.5 (4.2)	-18.0% (1.8)	-23.5 (-29.9, -17.2) *P*<0.001
	Placebo (n=34)	16.3 (3.4)	5.6% (2.7)	

[a]In hydrocortisone equivalents (4x equivalency factor for (methyl)predniso(lo)ne) 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.

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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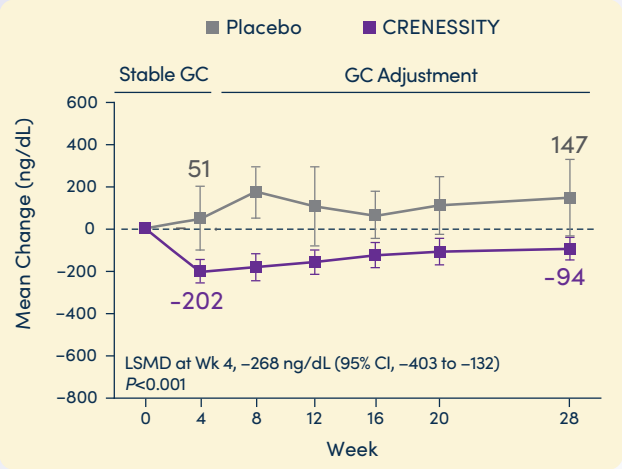
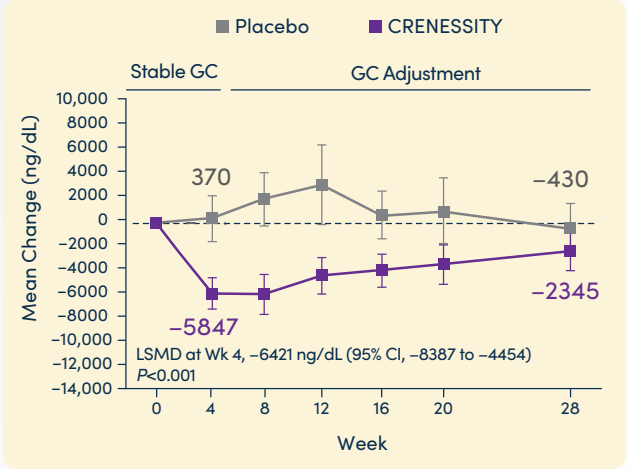
Change From Baseline in A4



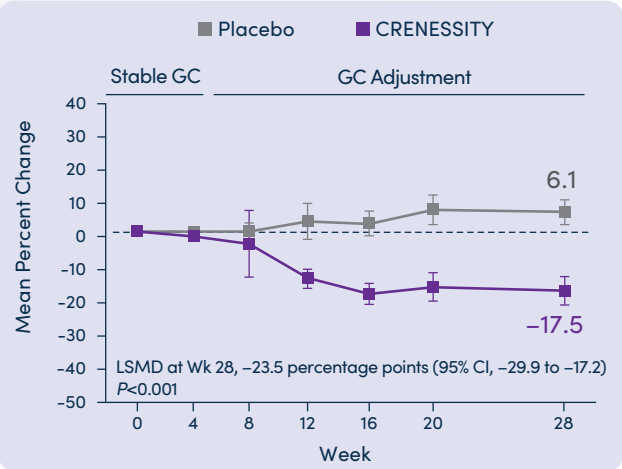
During the stable GC period, A4 levels decreased with CRENESSITY (−197 ng/dL) but increased with placebo (71 ng/dL) (LSMD, −268 ng/dL; *P*<0.001). At Week 28, after adjustments in the GC dose, the mean A4 level remained below baseline in the CRENESSITY group but was above baseline in the placebo group.

Change From Baseline in 17-OHP



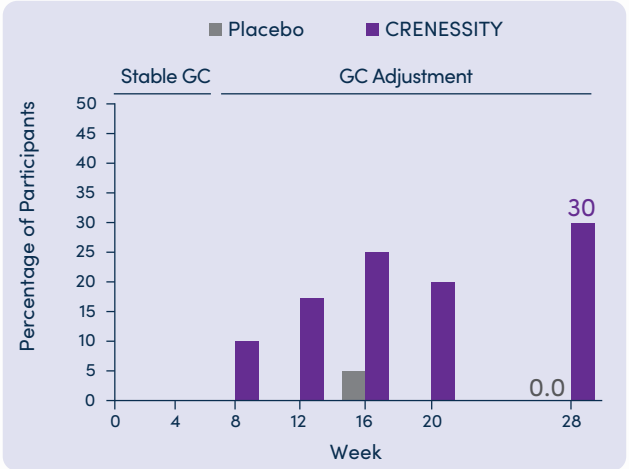
17-OHP decreased substantially from baseline to Week 4 in the CRENESSITY group and increased slightly in the placebo group (LSMD, −6421 ng/dL; *P*<0.001). Observed mean 17-OHP values at Week 4 were 2772 ng/dL in the CRENESSITY group and 9418 ng/dL in the placebo group.

Change From Baseline in GC While A4 Was Controlled



At Week 28, GC dose reduction while maintaining A4 levels was significantly greater among participants assigned to receive CRENESSITY than those in the placebo group (−18.0% vs 5.6%; LSMD, −23.5 percentage points; *P*<0.001). Observed mean GC doses at Week 28 were 12.8 mg/m^2/day in the CRENESSITY group and 17.0 mg/m^2/day in the placebo group.

Achievement of Physiologic GC Dose While A4 Was Controlled



Among CRENESSITY-treated participants, 30% achieved a physiologic GC dose of ≤11.0 mg/m^2/day in hydrocortisone dose equivalents at Week 28 while maintaining A4 levels, as compared with 0% in the placebo group.

17-OHP=17-hydroxyprogesterone; A4=androstenedione; CI=confidence interval; GC=glucocorticoid; LSMD=least-squares mean difference.

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

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 28 weeks (incidence ≥4% with CRENESSITY and more frequent than with placebo).[2]

Commonly Observed Adverse Reactions in Pediatric Patients

Adverse Reaction	Placebo (n=33)	CRENESSITY (n=69)
Headache	6%	25%
Abdominal pain	0%	13%
Fatigue	0%	7%
Nasal congestion	3%	7%
Epistaxis	0%	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]

The incidence of adrenal crisis was low and similar between participants in the CRENESSITY and placebo groups.[1,2] CRENESSITY does not address cortisol deficiency. Patients who are prescribed CRENESSITY should continue taking GCs. 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. In total, 100% of pediatric patients treated with CRENESSITY completed the 28-week, phase 3 trial (n=69). No patients discontinued due to an adverse event during the double-blind phase. Three patients discontinued the trial after Week 28. One patient withdrew their participation, and the other 2 patients discontinued treatment due to adverse events. One patient experienced body aches, upper abdominal pain, and nausea, which were considered by a local trial investigator to be unrelated to treatment. The other patient experienced nausea, dizziness, retching, and motion sickness, which were considered to be possibly related to treatment.[1]

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Summary of Findings

CRENESSITY significantly reduced adrenal androgens in pediatric patients with classic CAH and enabled an approximately 4x greater reduction in daily GC dose vs placebo.

- CRENESSITY significantly reduced serum A4 concentrations by −197 ng/dL at Week 4, compared with a 71 ng/dL increase in the placebo group (*P*<0.001)
- A substantial decrease in serum 17-OHP levels was observed, with a reduction of −5865 ng/dL in the CRENESSITY group vs an increase of 556 ng/dL in the placebo group (*P*<0.001)
- At Week 28, the GC dose was reduced by 18.0% in the CRENESSITY group, whereas the placebo group experienced a 5.6% increase (*P*<0.001)
- 30% of participants treated with CRENESSITY achieved physiologic GC dosing (≤11.0 mg/m^2/day) while maintaining control of A4 levels

In patients taking CRENESSITY, the most common adverse events included headache (25%), abdominal pain (13%), and fatigue (7%).

- No treatment-related serious adverse events occurred during the phase 3 trial
- Adverse events occurred in 84% of participants in the CRENESSITY group and 82% in the placebo group; these events were primarily mild to moderate in severity
- Serious adverse events were more common in the placebo group (12%) compared with the CRENESSITY group (1%)
- No difference was seen in the incidence of adrenal crisis between participants in the placebo group and the CRENESSITY group

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References

1. Sarafoglou K, Kim MS, Lodish M, et al. Phase 3 trial of CRENESSITY in pediatric congenital adrenal hyperplasia. *N Engl J Med.* 2024;391(6):493-503. doi:10.1056/NEJMoa2404655
2. CRENESSITY [package insert]. San Diego, CA: Neurocrine Biosciences, Inc.

NEUROCRINE® BIOSCIENCES

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