

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218808Orig1s000, 218820Orig1s000

INTEGRATED REVIEW

Integrated Review

Table 1. Application Information

Application type	NDA
Application number(s)	218808 218820
Priority or standard	Priority
Submit date(s)	4/29/2024
Received date(s)	4/29/2024
PDUFA goal date	12/29/2024
Division/office	Division of General Endocrinology (DGE)
Review completion date	12/12/2024
Established/proper name	Crinecerfont
(Proposed) proprietary name	CRENESSITY
Pharmacologic class	Corticotropin-releasing factor type 1 receptor antagonist
Other product name(s)	NBI-74788
Applicant	Neurocrine Biosciences Inc.
Dosage form(s)/formulation(s)	Oral capsule 25 mg, 50 mg, 100 mg Oral solution 50 mg/mL
Dosing regimen	100 mg bid for adults and pediatric patients ≥ 55 kg 50 mg bid for pediatric patients 4 years and older 20 - < 55 kg 25 mg bid for pediatric patients 4 years and older 10 - < 20 kg
Applicant-proposed indication(s)/population(s)	(b) (4)
SNOMED CT code for proposed indication disease term(s)¹	717261006 Classic congenital adrenal hyperplasia due to 21-hydroxylase deficiency
Regulatory action	Approval
Approved dosage (if applicable)	Same as above
Approved indication(s)/population(s) (if applicable)	CRENESSITY 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).
SNOMED CT code for approved indication disease term(s)¹	Same as above

¹ For internal tracking purposes only

Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms; bid, twice daily

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Glossary

A4	androstenedione
ACTH	adrenocorticotrophic hormone
ADME	absorption, distribution, metabolism, and excretion
AE	adverse event
ALT	alanine aminotransferase
AMP	adenosine monophosphate
ANC	absolute neutrophil count
ANCOVA	analysis of covariance
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
AUC	area under the concentration-time curve
AUC ₂₄	area under the concentration-time curve from 0 to 24 hours
AUC _{0-tlast}	area under the concentration-time curve from 0 to the time of the last measurable concentration
AUC _{0-∞}	area under the concentration-time curve from 0 to infinity
BCRP	breast cancer resistance protein
BE	bioequivalence
bid	twice daily
BSA	body surface area
BSEP	bile salt export pump
BTD	breakthrough therapy designation
CAH	congenital adrenal hyperplasia
cAMP	cyclic adenosine monophosphate
C _{avg}	average observed plasma concentration
CDER	Center for Drug Evaluation and Research
cDNA	complementary DNA
CFB	change from baseline
CFR	Code of Federal Regulations
CI	confidence interval
CL _{int}	intrinsic clearance
C _{max}	maximum observed plasma concentration
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
C _{min}	minimum observed plasma concentration
CNS	central nervous system
COC	combined oral contraceptives
COVID	coronavirus disease
CPK	creatine phosphokinase
CRF	corticotropin-releasing factor
CRF1	corticotropin-releasing factor type 1
CSS	controlled substance staff
C-SSRS	Columbia-Suicide Severity Rating Scale

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C_{trough}	trough plasma concentration
CV	coefficient of variation
CYP	cytochrome P450
CWRES	conditional weighted residuals
DARRTS	Document Archiving, Reporting, and Regulatory Tracking System
DB	double-blind
DDI	drug-drug interaction
DGE	Division of General Endocrinology
DMEPA	Division of Medication Error Prevention and Analysis
DPMH	Division of Pediatrics and Maternal Health
DPSS	descriptive pregnancy safety study
EC_{50}	half-maximal effective concentration
ECG	electrocardiogram
EFD	embryo-fetal development
eGFR	estimated glomerular filtration rate
E_{max}	maximum drug effect
E-R	exposure-response
ETA	random effects
FAO	Food and Agriculture Organization
FAS	full analysis set
FDA	Food and Drug Administration
f_m	fraction metabolized
FMQ	FDA medical query
F_{rel}	relative bioavailability
GC	glucocorticoid
GD	gestation day
GI	gastrointestinal
GLP	good laboratory practice
GMR	geometric mean ratio
HCl	hydrochloride
HEK	human embryonic kidney
hERG	human ether-à-go-go-related gene
HOMA-IR	homeostatic model assessment for insulin resistance
IC_{50}	half-maximal inhibitory concentration
ICH	International Council for Harmonisation
IID	Inactive Ingredient Database
IND	investigational new drug
INR	international normalized ratio
IRT	interdisciplinary review team
IV	intravenous(ly)
K_a	absorption rate constant
KI	concentration of inhibitor that gives half-maximal rate of inactivation
K_i	inhibitor constant
K_{inact}	maximal rate of enzyme inactivation
K_m	dissociation constant of the enzyme-substrate complex
LC-MS/MS	liquid-chromatography tandem mass spectroscopy

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LS	least-squares
MATE	multidrug and toxin extrusion transporter
MDCKII	Madin-Darby canine kidney type II
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	maximum recommended human dose
mRNA	messenger ribonucleic acid
NADPH	nicotinamide adenine dinucleotide phosphate
NCT	National Clinical Trial
NDA	new drug application
NHANES	National Health and Nutrition Examination Survey
NOAEL	no-observed-adverse-effect level
NONMEM	nonlinear mixed-effects modeling
NPDE	normalized prediction distribution errors
OAT	organic anion transporter
OATP	organic anion transporting polypeptide
OCS	oral contraceptive steroids
OCT	organic cation transporter
17-OHP	17-hydroxyprogesterone
OPQ	Office of Pharmaceutical Quality
OSI	Office of Scientific Investigations
P _{app}	apparent permeability coefficient
P-gp	P-glycoprotein
PD	pharmacodynamic
PET	polyethylene terephthalate
PG	propylene glycol
PI	prescribing information
PK	pharmacokinetic
PMR	postmarketing requirement
PND	postnatal day
PO	oral(ly)
popPK	population pharmacokinetic
PRA	plasma renin activity
PT	prothrombin time
PTT	partial thromboplastin time
qAM	every morning
qPM	every evening
QT _c	corrected QT
QT _{cF}	QT interval corrected for heart rate using Fridericia's correction
RSE	relative standard error
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
(b) (4)	
SE	standard error
(b) (4)	
SEE	substantial evidence of effectiveness

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SEM	standard error of the mean
SOC	system organ class
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TK	toxicokinetic
$T_{\max}$	time to maximum observed plasma concentration
TSH	thyroid stimulating hormone
TTC	threshold of toxicological concern
ULN	upper limit of normal
$V_{\max}$	maximal velocity
VPC	visual predictive check
WBC	white blood cell
WHO	World Health Organization

I. Executive Summary

7. Overview

7.1. Summary of Regulatory Action

Patients with classic congenital adrenal hyperplasia (CAH) have decreased cortisol synthesis due to an enzymatic defect in the adrenal gland that leads to increases in adrenocorticotrophic hormone (ACTH) and adrenal stimulation, causing excess androgen production. Patients typically require supraphysiologic glucocorticoid dosages to reduce ACTH and control the excess androgens. The excess glucocorticoid and uncontrolled androgens cause a variety of adverse effects. Crinecerfont inhibits ACTH secretion by the pituitary. The Applicant, Neurocrine Biosciences Inc., submitted this marketing application for crinecerfont (proposed trade name CRENESSITY) (b) (4)

Crinecerfont has fast track, breakthrough therapy, and orphan designations and was granted priority review.

The application contains two adequate and well-controlled clinical investigations in classic CAH—one in adults and the other in children 4 years of age and older. These trials clearly met their efficacy objectives, demonstrating androgen control in the setting of reduced glucocorticoid dosing, a clinical benefit given the known adverse effects of excess glucocorticoid use. The review team did not identify any major efficacy issues.

The safety of crinecerfont is adequately characterized in the context of this rare disease. Risks include hypersensitivity reactions, adrenal insufficiency/crisis (if an inadequate dose of glucocorticoid is used, including during times of stress/illness), and tolerability issues (e.g., headache, fatigue). There is also a finding of mild reductions in neutrophil counts, which were not associated with an increased risk of infection, may possibly be related to reductions in glucocorticoid dosages, and are of unclear clinical significance. The trials had 2:1 randomization. Three crinecerfont-treated subjects versus one placebo-treated subject in the adult trial and four crinecerfont-treated subjects versus no placebo-treated subjects in the pediatric trial had an increase in suicidal ideation assessed using the Columbia-Suicide Severity Rating Scale. An adult on crinecerfont also had a suicide attempt. The relationship of these findings to crinecerfont is unclear given the very low event rates, remote history of suicidality in some of the subjects who had an increase in their Columbia-Suicide Severity Rating Scale, lack of neuropsychiatric findings in animals, and no increase in suicidality when crinecerfont was studied in a major depressive disorder trial. All these risks and uncertainties will be mitigated with labeling, and we will continue to monitor these risks in the postmarketing setting.

Existing human data regarding crinecerfont use during pregnancy and lactation are insufficient to inform risks with these uses; therefore, we are requiring further assessment in these settings as postmarketing requirements.

The entire review team and signatory authority agree that the application can be approved. There were no areas of scientific or regulatory disagreement. The overall benefit-risk is favorable as described in the benefit-risk framework below.

7.2. Conclusions on Substantial Evidence of Effectiveness

Substantial evidence of effectiveness (SEE) was established with two or more adequate and well-controlled clinical investigations.

Substantial evidence of effectiveness was established based on the two pivotal, phase 3, double-blind, placebo-controlled efficacy trials, Trial NBI-74788-CAH3003 (Trial CAH3003, National Clinical Trial [NCT] 04490915) conducted in adults with classic CAH, and NBI-74788-CAH2006 (Trial CAH2006, NCT 04806451) conducted in pediatric subjects aged 4 to 17 years, inclusive, with classic CAH. In both studies, crinecerfont had a statistically significant greater effect than placebo on the primary efficacy endpoint, as described below. In Trial CAH3003, crinecerfont also had a statistically significantly greater effect on the key secondary efficacy endpoints of change from baseline in serum androstenedione level at Week 4 and the proportion of subjects with a reduction to physiologic glucocorticoid dose while maintaining androstenedione control at Week 24. In pediatric Trial CAH2006, crinecerfont was statistically significantly better than placebo for both key secondary efficacy endpoints (i.e., change from baseline in serum 17-hydroxyprogesterone at Week 4 and the percentage change in daily glucocorticoid dose while maintaining androstenedione control at Week 28).

The order of the primary and key secondary efficacy endpoints differed in the two trials. Data are presented as least-squares means with standard error of the mean or 95% confidence interval in parentheses. In the adult trial, CAH3003, crinecerfont resulted in a significantly greater mean percent change from baseline in glucocorticoid daily dose at Week 24 while androstenedione (A4) levels were controlled (i.e., $A4 \leq 120\%$ of baseline or $\leq$ upper limit of normal (ULN) for age and sex), which was the primary efficacy endpoint. Crinecerfont allowed for lowering of the glucocorticoid daily dose by 27% (2.4) compared to 10% (3.2) in the placebo group at Week 24 while androstenedione levels were controlled. The treatment difference was -17% (95% confidence interval [CI]: -24, -10). Serum androstenedione at Week 4 was a key secondary endpoint and significantly decreased by 299 (37.7) ng/dL compared to an increase of 46 (51.0) ng/dL in the placebo group. The treatment difference was -366 ng/dL (95% CI: -457, -232). In addition, 63% of subjects receiving crinecerfont compared to 18% in the placebo group were able to reduce their daily glucocorticoid dose to the physiologic range (i.e., dose < 11 mg/m²/day hydrocortisone equivalents) while maintaining androstenedione control at Week 24.

In the pediatric Trial CAH2006, the primary efficacy endpoint was change in serum androstenedione at Week 4. Crinecerfont significantly lowered serum androstenedione levels -197 (39.4) ng/dL, compared to an increase of 71 (56.2) ng/dL for the placebo group at Week 4 while glucocorticoid dosage remained stable. The treatment difference was -268 (95% CI: -403, -132). Key secondary endpoints included percent change in glucocorticoid daily dose at Week 28 while androstenedione levels were controlled and change from baseline in serum 17-hydroxyprogesterone at Week 4. In subjects receiving crinecerfont, glucocorticoid daily dose was lowered by 18% (1.8) compared to an increase of 6% (2.6) in the placebo group at Week 28 while androstenedione levels were controlled. The treatment difference was -24% (95% CI: -30, -17). Additionally, crinecerfont lowered 17-hydroxyprogesterone levels at Week 4 by 5865 ng/dL (compared to an increase of 556 ng/dL in the placebo group).

In summary, these trials compellingly demonstrated that crinecerfont allowed for adrenal androgen control with decreasing doses of glucocorticoids. In fact, many subjects achieved physiologic glucocorticoid dosing with continued androgen control. The significant decrease in glucocorticoid dose is clinically meaningful because lowering glucocorticoid dose can have a direct impact on the subsequent adverse events associated with glucocorticoid excess.

8. Benefit-Risk Assessment

8.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	- Classic congenital adrenal hyperplasia (CAH) is a rare, life-threatening condition most commonly caused by deficiency of the adrenal enzyme 21-hydroxylase. - Newborn screening includes testing for CAH, so affected individuals are usually identified at birth. - Features of CAH include adrenal insufficiency from decreased cortisol synthesis (with or without aldosterone deficiency), loss of negative feedback causing increases in adrenocorticotrophic hormone (ACTH) secretion, and ACTH-mediated adrenal stimulation, leading to excess adrenal androgens. Androstenedione and 17-hydroxyprogesterone levels are measured clinically as markers of disease control. - Elevated androgen levels cause hirsutism, acne, subfertility (in females), and short adult stature (because of accelerated growth in childhood and premature epiphyseal fusion). - Glucocorticoid deficiency can lead to adrenal insufficiency or adrenal crisis if not adequately treated and also results in elevated ACTH levels, promoting growth of testicular adrenal rest tumors, which may cause subfertility in males.	Classic congenital adrenal hyperplasia is a rare, life-threatening condition that is typically identified at birth and is most commonly caused by deficiency of 21-hydroxylase. This enzyme deficiency causes adrenal insufficiency and excess adrenal androgen production. Adrenal insufficiency can lead to an adrenal crisis. Elevated androgen levels cause hirsutism, acne, subfertility (in females), and short adult stature (because of accelerated growth in childhood and premature epiphyseal fusion). Glucocorticoid deficiency results in elevated adrenocorticotrophic hormone levels, promoting growth of testicular adrenal rest tumors, which may cause subfertility in males.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	- The standard-of-care treatment for the adrenal insufficiency aspect of CAH includes glucocorticoid replacement (e.g., hydrocortisone) and mineralocorticoid replacement (fludrocortisone). - Stress dosing of glucocorticoids is needed for acute illness and other situations associated with increased cortisol requirements. - Suppression of excess adrenal androgen is achieved with physiologic glucocorticoid dosages in some patients, but many patients require supraphysiologic dosages of glucocorticoid to achieve androgen control. - Chronic exposure to supraphysiologic glucocorticoid has adverse effects on body weight, metabolic parameters, and bone health.	Standard-of-care therapy includes glucocorticoid and mineralocorticoid replacement. Additional glucocorticoid is often needed to suppress elevated adrenal androgen levels, and this supraphysiologic glucocorticoid can have long-term adverse effects on body weight, metabolic parameters, and bone health.
Benefit	- By reducing ACTH production via corticotropin-releasing factor-1 receptor antagonism, crinecerfont lowers adrenal androgen levels so that the disease can be managed with lower, more physiologic, total daily glucocorticoid dosages. - In two phase 3 trials, one in adults and one in pediatric subjects (aged 4 to 17 years) with CAH, crinecerfont significantly lowered adrenal androgen levels at Week 4 while glucocorticoid dosage remained stable, and allowed for a significant decrease in glucocorticoid daily dosage at Week 24 (adult trial) or Week 28 (pediatric trial) while androgen levels were controlled. - Crinecerfont lowered androstenedione levels at Week 4 by 299 ng/dL (compared to an increase of 46 ng/dL in the placebo group) in the adult trial and by 197 ng/dL (compared to an increase of 80 ng/dL in the placebo group) in the pediatric trial. - Crinecerfont lowered 17-hydroxyprogesterone levels at Week 4 by 5865 ng/dL (compared to an increase of 556 ng/dL in the placebo group) in the pediatric trial.	In adult and pediatric subjects aged 4 years and older with CAH, crinecerfont allowed for adrenal androgen control at lower glucocorticoid dosages, many at physiologic or near-physiologic replacement dosages. Decreased exposure to supraphysiologic glucocorticoid is clinically meaningful because excess glucocorticoid has adverse effects on body weight, metabolic parameters, and bone health. Changes in body weight and metabolic parameters were not improved compared to placebo after 24 weeks of crinecerfont treatment in adults.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- Crinecerfont allowed for lowering of the glucocorticoid daily dose by 27.3% (compared to 10.3% in the placebo group) at Week 24 in the adult trial and 18% at Week 28 (compared to an increase of 5.6% in the placebo group) in the pediatric trial while androstenedione levels were controlled. - In the crinecerfont group, 62.7% of subjects (versus 17.5% in the placebo group) in the adult study and 29.9% of subjects (versus none in the placebo group) in the pediatric study achieved a glucocorticoid dose in the physiologic range (i.e., ≤ 11 mg/m²/day hydrocortisone equivalents adjusted for body surface area) at Weeks 24 and 28, respectively, while androstenedione levels were controlled. - Change from baseline at Week 24 in HOMA-IR, body weight, and total fat mass in the adult trial were not statistically significantly different from placebo.	
Risk and risk management	- The crinecerfont safety database was adequate in size and scope in the context of this rare disease. Adverse reactions were generally considered tolerability issues (e.g., headache, fatigue) that can be adequately addressed with labeling. - Decreased neutrophil counts ($< 2 \times 10^3$ cells/μL, but generally $> 1 \times 10^3$ cells/μL) occurred more frequently in study subjects treated with crinecerfont compared to placebo during the double-blind treatment periods of both the adult (14.2% versus 5.2%) and pediatric (36.8% versus 15.6%) trials. These mild decreases, which were not associated with an increased risk of infection in the trials, may possibly be related to reductions in glucocorticoid dosages, and are of unclear clinical significance.	Postmarketing requirements for a descriptive pregnancy safety study and a clinical lactation study to determine the extent to which crinecerfont is present in human milk are warranted. The observations of mildly decreased neutrophil counts and positive findings on the Columbia-Suicide Severity Rating Scale, including the one suicide attempt, in those taking crinecerfont will be described in the Adverse Reactions section of the product label so that prescribers are aware of the findings. We will continue to monitor for these adverse events in the postmarketing setting and require that the Applicant implement enhanced pharmacovigilance for adverse events of suicidality and neutropenia. Product labeling will include a Warning regarding the need for increased glucocorticoid doses in the setting of concurrent illness or other physiologic stressors.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	In the adult trial, 3 (2.5%) of 120 crinecerfont-treated subjects and 1 (1.7%) of the 58 placebo-treated subjects reported suicidal ideation on the Columbia-Suicide Severity Rating Scale during the 24-week double-blind treatment period. One crinecerfont-treated subject attempted suicide. In the pediatric trial, 4 (6%) of 67 crinecerfont-treated subjects and none of the 31 placebo-treated subjects reported suicidal ideation on the Columbia-Suicide Severity Rating Scale during the 28-week double-blind treatment period. The relationship of these findings to study drug is unclear, given the very low event rates, remote history of suicidality in some of the subjects who had an increase on their Columbia-Suicide Severity Rating Scale, lack of neuropsychiatric findings in animals, and no increase in suicidality when crinecerfont was studied in a depression trial. • Serious adverse events of acute adrenal insufficiency occurred in both the adult and pediatric trials in subjects receiving crinecerfont. These cases occurred in the setting of physiologic stress (most commonly underlying infection) with insufficient adjustment of corticosteroid dose, and were not caused by crinecerfont itself. • Human data regarding crinecerfont use during pregnancy and lactation are insufficient to inform the risks in labeling.	

Abbreviations: ACTH, adrenocorticotrophic hormone; CAH, congenital adrenal hyperplasia; HOMA-IR, homeostatic model assessment of insulin resistance

8.2. Conclusions Regarding Benefit-Risk

Classic congenital adrenal hyperplasia is a rare disease most commonly caused by deficiency of the adrenal enzyme 21-hydroxylase. The lack of 21-hydroxylase activity results in deficiencies of cortisol and, in some cases, aldosterone. Because the adrenal gland tries to compensate for the lack of cortisol production, excessive adrenal androgens are produced. Glucocorticoid replacement is necessary for the underlying adrenal insufficiency associated with CAH. Additionally, mineralocorticoid replacement may be needed. Treatment of the excessive adrenal androgen production associated with CAH can be challenging and generally requires glucocorticoid dosing that exceeds the needed physiologic replacement. Therefore, control of adrenal androgens with supraphysiologic glucocorticoid dosing can be associated with adverse effects on body weight, growth, metabolic parameters, and bone health.

Crinecerfont is a selective antagonist of the corticotropin-releasing factor type 1 (CRF1) receptor intended to decrease ACTH stimulation of the adrenal gland's hormone production. This is a novel approach to allow for control of adrenal androgen production as an adjunct to the required physiologic glucocorticoid therapy for treatment of the underlying adrenal insufficiency.

The Applicant conducted two adequate and well-controlled clinical trials in the CAH population: one in adults and one in pediatric subjects aged 4 years and older. These trials demonstrated that crinecerfont allowed for adrenal androgen control with decreasing doses of glucocorticoids. In fact, many subjects achieved physiologic glucocorticoid dosing with continued androgen control. The significant decrease in glucocorticoid dose is clinically meaningful because lowering glucocorticoid dose can have a direct impact on the subsequent adverse events associated with glucocorticoid excess.

The safety profile of crinecerfont was adequately characterized in the context of this rare disease. Based on crinecerfont's mechanism of action, adrenal insufficiency was a clinical concern and was monitored throughout the development program. Cases of adrenal insufficiency, some with fatality, did occur in the setting of stress situations for subjects. The adrenal insufficiency and crisis were not caused by crinecerfont itself but the underlying disease state. Therefore, patients will need to continue physiologic glucocorticoid replacement and to be advised of the need for increased glucocorticoid doses as the time of stress from concurrent illness or other reasons. This will be addressed in product labeling as a Warning and Precaution.

Crinecerfont was previously evaluated as a treatment for depression, and the activity of crinecerfont on the CRF receptors in the pituitary indicate that the drug crosses the blood-brain barrier. Therefore, the clinical development program assessed the risk of suicide with the use of the Columbia Suicide Severity Rating Scale (C-SSRS). One subject in the adult trial attempted suicide during the conduct of the trial. The assessment of the C-SSRS in the adult trial revealed 3/120 subjects in the crinecerfont group and 1/58 subjects in the placebo group reported suicidal ideation, evident by an increase in their C-SSRS score. In the pediatric trial, 4/67 subjects in the crinecerfont group and 0/31 subjects in the placebo group increased their C-SSRS score. The relationship of these findings to study drug is unclear, given the very low event rates, remote history of suicidality in some of the subjects who had an increase on their Columbia-Suicide Severity Rating Scale, lack of neuropsychiatric findings in animals, and no increase in suicidality when crinecerfont was studied in a major depressive disorder trial.

Neutropenia was observed in a phase 2 study of crinecerfont for major depressive disorder. In the adult and pediatric CAH studies, decreased neutrophil counts also occurred more frequently in study subjects treated with crinecerfont compared to placebo. The etiology for this is unclear and the findings were not associated with increased risk of infection.

Hypersensitivity reactions, including angioedema, were reported with crinecerfont treatment. Other noted adverse reactions (e.g., headache, fatigue) may be tolerability issues.

In summary, crinecerfont use as an adjunct to glucocorticoid therapy has been shown to reduce androgen levels in adults and pediatric subjects with CAH and lower glucocorticoid dose requirements, with many subjects able to achieve physiologic or near-physiologic glucocorticoid replacement doses. The decreased exposure to supraphysiologic glucocorticoid is clinically beneficial because of the well-known adverse effects of excess glucocorticoid. The safety profile is adequately characterized, and risks (e.g., adverse reactions such as headache and fatigue; contraindication if prior hypersensitivity reaction to crinecerfont; need for adequate glucocorticoid replacement to avoid adrenal insufficiency/crisis) can be adequately addressed through product labeling. Other findings of unclear clinical significance (e.g., minor neutrophil count reductions) and unclear relation to study drug (e.g., suicidality) will be included in labeling for prescriber awareness. These risks and uncertainties are outweighed by the benefits when crinecerfont is used according to the approved labeling.

II. Interdisciplinary Assessment

9. Introduction

Crinecerfont, a new molecular entity, is a first-in-class selective antagonist of the pituitary corticotropin-releasing factor type 1 (CRF1) receptor. The Applicant submitted two crinecerfont NDAs (for two formulations) for the proposed indication (b) (4)

caused by 21-hydroxylase deficiency:

- NDA 218808 for soft gelatin capsules (25 mg, 50 mg, 100 mg)
- NDA 218820 for oral solution (50 mg/mL)

The proposed dosing regimen is:

- 100 mg twice daily for adults (aged 18 years and older)
- 100 mg twice daily for pediatric patients weighing greater than or equal to 55 kg
- 50 mg twice daily for pediatric patients weighing 20 kg to less than 55 kg
- 25 mg twice daily for pediatric patients weighing 10 kg to less than 20 kg

In patients with classic CAH, deficiency of 21-hydroxylase enzymatic activity causes deficiency of adrenal glucocorticoid (cortisol) and mineralocorticoid (aldosterone) production. The glucocorticoid deficiency stimulates excess adrenocorticotrophic hormone (ACTH) production from the pituitary gland, which stimulates the adrenal cortex to produce excess androgens. Levels of androstenedione (A4) and 17-hydroxyprogesterone (17-OHP) are measured clinically as biomarkers of adrenal androgen production and disease control in patients with CAH.

Standard of care treatment of classic CAH consists of glucocorticoid (e.g., hydrocortisone) and mineralocorticoid (fludrocortisone) replacement. Exogenous glucocorticoids remedy adrenal insufficiency as well as suppress excess adrenal androgen production, while mineralocorticoids are used to correct salt-wasting in the setting of insufficient aldosterone production. While physiologic glucocorticoid doses are required to remedy adrenal insufficiency, supraphysiologic glucocorticoid dosages are often necessary to suppress the high ACTH levels and control adrenal androgen production.

The use of supraphysiologic glucocorticoid doses creates a clinical management challenge of balancing disease control (by lowering adrenal androgen levels) with avoiding iatrogenic Cushing's syndrome due to excess glucocorticoid exposure. Elevated androgen levels cause hirsutism, acne, subfertility (in females), and short adult stature (because of accelerated growth in childhood and premature epiphyseal fusion). Elevated ACTH levels promote growth of testicular adrenal rest tumors, which may cause subfertility in males. Long-term exposure to excess glucocorticoid causes weight gain and adverse effects on metabolism, the cardiovascular system, bone health, and growth (in children) ([Merke and Auchus 2020](#)).

The Applicant hypothesizes that by reducing pituitary ACTH production via CRF1 receptor antagonism, crinecerfont lowers adrenal androgen levels so that the disease can be managed with

lower, more physiologic, total daily glucocorticoid dosages (Table 3). By reducing daily glucocorticoid requirements, crinecerfont treatment as an adjunct to glucocorticoid replacement ultimately minimizes the adverse health consequences of long-term exposure to supraphysiologic glucocorticoid.

Table 3. Comparison of Standard of Care to Crinecerfont Treatment

Treatment Aspect	Standard of Care	Crinecerfont
Additional androgen-lowering (if needed)	Additional glucocorticoid	Crinecerfont
Physiologic glucocorticoid replacement	Physiologic glucocorticoid dosage	Physiologic glucocorticoid dosage
Mineralocorticoid replacement	Fludrocortisone	Fludrocortisone

Source: Clinical reviewer generated

The Applicant submitted data from two pivotal phase 3, randomized, double-blind, placebo-controlled trials (with open-label extension periods) supporting the efficacy and safety of crinecerfont in adult (Trial CAH3003) and pediatric (Trial CAH2006) subjects with classic CAH. The randomized, double-blind, placebo-controlled period lasted 24 weeks in the adult study and 28 weeks in the pediatric study. The open-label extension period continued through 12 months (52 weeks in the pediatric study).

Primary and key secondary endpoints for Trial CAH3003 include:

- Primary: Percent change from baseline in glucocorticoid daily dose at Week 24 while Week 24 androstenedione levels are controlled ($\leq 120\%$ of baseline or $\leq$ upper limit of normal [ULN] for age and sex)
- First key secondary: Change from baseline in serum androstenedione level at Week 4 while glucocorticoid dose is stable
- Second key secondary: Proportion with reduction in glucocorticoid daily dose to ≤ 11 mg/m²/day hydrocortisone equivalent at Week 24 while androstenedione levels are controlled ($\leq 120\%$ of baseline or $\leq$ ULN for age and sex)
- Additional key secondary: Changes from baseline in homeostatic model assessment for insulin resistance (HOMA-IR), weight, and fat mass at Week 24

Primary and key secondary endpoints for Trial CAH2006 include:

- Primary: Change from baseline in serum androstenedione level at Week 4 while glucocorticoid dose is stable
- First key secondary: Change from baseline in serum 17-hydroxyprogesterone level at Week 4 while glucocorticoid dose is stable
- Second key secondary: Percent change from baseline in glucocorticoid daily dose at Week 28, while Week 28 androstenedione levels are controlled ($\leq 120\%$ of baseline or $\leq$ ULN for sex and age or, if pubertal, pubertal stage).

Crinecerfont has Orphan (March 15, 2019), Fast Track (June 15, 2021), and Breakthrough Therapy (December 1, 2023) designations. Crinecerfont met breakthrough therapy designation criteria because the Applicant submitted preliminary clinical data showing that the drug may provide a substantial improvement over available therapy based on statistically significant

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reductions in total daily glucocorticoid dose requirements (in many cases to physiologic doses) while maintaining control of adrenal androgen levels with crinecerfont compared to placebo.

9.1. Review Issue List

9.1.1. Key Efficacy Review Issues

9.1.1.1. Appropriate Dosage in Pediatric Patients Weighing 10 kg to Less Than 20 kg

9.1.2. Key Safety Review Issues

Key safety review issues were identified based on the drug's mechanism of action as well as safety data from the clinical development program in major depressive disorder. Refer to Section [13.7](#) for in depth discussion of these concerns.

9.1.2.1. Potential for Adrenal Insufficiency

9.1.2.2. Potential for Hypersensitivity

9.1.2.3. Potential for Neutropenia and Reduction in Total White Blood Cell Count

9.1.2.4. Neuropsychiatric Safety Concerns

9.2. Approach to the Clinical Review

Trial CAH3003 in adults with classic CAH and Trial CAH2006 in pediatric subjects aged 4 to 17 years with classic CAH are the pivotal phase 3 trials reviewed as primary evidence of crinecerfont's efficacy and safety ([Table 4](#)). Crinecerfont was evaluated in a double-blind, placebo-controlled fashion for 24 weeks (Trial CAH3003) or 28 weeks (Trial CAH2006), followed by an open-label treatment period through 12 months (both trials). These trials are fit for purpose to support this application.

Efficacy results submitted for Trial CAH3003 include analysis of the completed double-blind period (Day 1 to Week 24) and an interim analysis for the ongoing open-label period (Week 24 to Month 12) at the data cutoff (July 19, 2023). Efficacy results submitted for Trial CAH2006 include analysis of the completed double-blind period (Day 1 to Week 28) and an interim analysis of the available data for the ongoing open-label period (Week 28 to Week 52) at the data cutoff (August 9, 2023). Data from the 120-Day Safety Update were incorporated into the review.

We also independently reviewed the literature and the literature review submitted by the Applicant justifying the clinical meaningfulness of the studies' efficacy findings.

The safety review focused on results from the two phase 3 trials in subjects with CAH, with supportive data on any signal identified in the CAH population from a phase 2 study in subjects with major depressive disorder. Two phase 2 dose-finding trials of crinecerfont in adults with CAH (Trial CAH2001) and pediatric subjects with CAH (Trial CAH2008) were used, together with other available information, to select the doses for the phase 3 trials.

9.3. Approach To Establishing Substantial Evidence of Effectiveness

Select from the options below to indicate how substantial evidence of effectiveness (SEE) was established (if applicable). If there are multiple indications, repeat items 1–3 for each indication.

1. Verbatim indication:

CRENESSITY is a corticotropin-releasing factor type 1 receptor antagonist 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).

2. SEE was established with

a. Adequate and well-controlled clinical investigation(s):

- i. ☒ Two or more adequate and well-controlled clinical investigations, **OR**
- ii. ☐ One adequate and well-controlled clinical investigation with highly persuasive results that is considered to be the scientific equivalent of two clinical investigations

OR

b. ☐ One adequate and well-controlled clinical investigation and confirmatory evidence^{1,2,3}

OR

c. ☐ Evidence that supported SEE from a prior approval (e.g., 505(b)(2) application relying only on a previous determination of effectiveness; extrapolation; over-the-counter switch)²

3. Complete response, if applicable

- a. ☐ SEE was established
- b. ☒ SEE was not established (*if checked, omit item 2*)

¹ FDA draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* ([December 2019](#))

² FDA guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products* ([May 1998](#))

³ FDA guidance for industry *Demonstrating Substantial Evidence of Effectiveness Based on One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* ([September 2023](#))

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Table 4. Clinical Trials Submitted¹ in Support of Efficacy and Safety Determinations for Crinecerfont

Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
NBI-74788-CAH3003	Adults with classic CAH due to 21-hydroxylase deficiency	Control type: placebo concurrent Randomization: stratified randomization Randomization ratio: 2:1 Blinding: Double-blind Biomarkers: Yes (androstenedione) Innovative design features: None	Drug: Crinecerfont Dose: 100 mg bid Number treated: 181 Duration: DB period: 24 weeks OL period: 24 weeks	Primary: • Percent CFB in glucocorticoid daily dose at Week 24 while androstenedione was adequately controlled at $\leq 120\%$ of baseline or $\leq \text{ULN}$ for age and sex Secondary: • CFB in serum androstenedione at Week 4 • Achievement of a reduction in glucocorticoid daily dose to physiologic levels at Week 24 • CFB in HOMA-IR (in fasting subjects not on insulin) at Week 24 • Percent CFB in weight at Week 24 • CFB in percent total fat mass at Week 24	Planned: 165 Actual: 182	Centers: 54 Countries: 16

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Trial Identifier	Trial Population	Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	No. of Subjects Planned; Actual Randomized	No. of Centers and Countries
NBI-74788-CAH2006	Children ages 4 to 17 years with classic CAH due to 21-hydroxylase deficiency	Control Type: Placebo concurrent Randomization: stratified randomization Randomization ratio: 2:1 Blinding: Double-blind Biomarkers: Yes (androstenedione, 17-OHP) Innovative design features: None	Drug: Crinecerfont Dose: 25 mg bid (10 to <20 kg) 50 mg bid (20 to <55 kg) 100 mg bid (≥55 kg) Number treated: 102 Duration: DB Period: 28 weeks OL Period: 24 weeks	Primary: - CFB in serum androstenedione at Week 4 Secondary: - CFB in serum 17-OHP at Week 4 - Percent CFB in glucocorticoid daily dose at Week 28 while serum androstenedione was ≤120% of the baseline value or ≤ULN, according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5)	Planned: 81 Actual: 103	Centers: 37 Countries: 10

Source: Clinical Study Report and adsl.xpt

¹ Includes all submitted clinical trials, even if not reviewed in-depth, except for phase 1 and pharmacokinetic studies.

Abbreviations: 17-OHP, 17-hydroxyprogesterone; bid, twice daily; CAH, congenital adrenal hyperplasia; CFB, change from baseline; DB, double-blind; HOMA-IR, homeostatic model assessment of insulin resistance; No., number; OL, open-label; qAM, every morning; ULN, upper limit of normal

10. Patient Experience Data

The Applicant submitted patient-reported outcome data for both Trials CAH3003 and CAH2006, which we considered exploratory. Patient-reported outcomes for Trial CAH3003 were assessed on the 36-Item Short Form Health Survey, EuroQol 5 Dimensions 5 Levels, Multidimensional Assessment of Fatigue, Psychological General Well-Being Index, and Medical Outcomes Study 12-Item Sleep Scale. Patient- and caregiver-reported outcomes for Trial CAH2006 were assessed on the EuroQol 5 Dimensions Youth, EuroQol 5 Dimensions Levels, EuroQol Visual Analog Scale, and Pediatric Quality of Life Instrument. The patient-reported outcome data are not discussed in the review because their validity in the proposed study population has not been shown, and none were subject to statistical hypothesis testing.

Table 5. Patient Experience Data Submitted or Considered
Data Submitted in the Application

Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

11. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

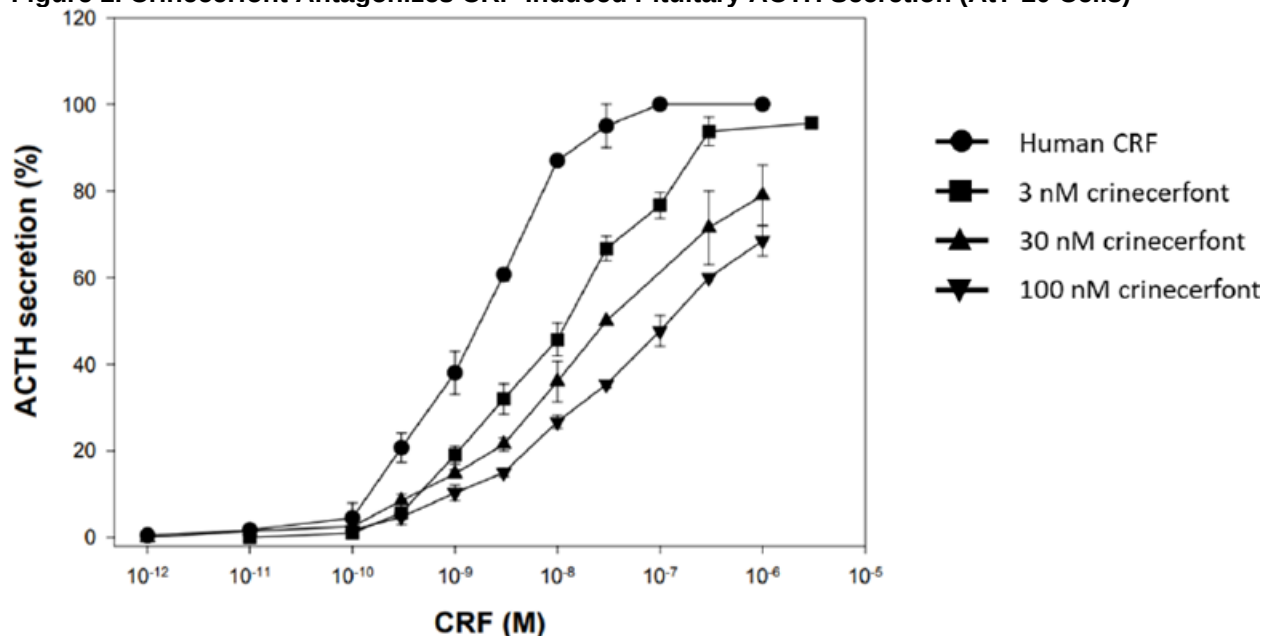
11.1. Nonclinical Assessment of Potential Effectiveness

Cortisol (glucocorticoid) deficiency in patients with CAH causes an increase in corticotropin-releasing factor (CRF) hormone from the hypothalamus, which stimulates excessive adrenocorticotrophic hormone (ACTH) secretion from the anterior pituitary. Excessive ACTH secretion stimulates the adrenal cortex, which leads to adrenal hyperplasia.

Crinecerfont is a selective first-in-class CRF1 receptor antagonist that reduces the excess ACTH secretion caused by elevated CRF in response to low glucocorticoid levels in patients with CAH. The Applicant provided a series of in vitro and in vivo nonclinical pharmacology studies to demonstrate that crinecerfont binds CRF1 receptors and inhibits CRF-induced cyclic adenosine monophosphate (cAMP) synthesis and ACTH release. The nonclinical pharmacology data were provided to support the proposed mechanism of action of crinecerfont.

Crinecerfont inhibited the ability of CRF to bind human and rodent CRF1 receptors with half-maximal inhibitory concentration (IC_{50}) values of 0.6 to 3.99nM and showed no affinity for related receptors human CRF2a or human CRF-binding protein (limited to 11.5% inhibition at 10 μ M crinecerfont). The most abundant crinecerfont metabolite (NBI-756179, M6), which represented 6% of human crinecerfont exposure, bound to CRF1 receptors with nanomolar affinity (K_i =1.14nM), but no inhibitor constant (K_i) was provided for crinecerfont. The contribution of this metabolite to CRF1 receptor antagonist activity was considered minor due to its low abundance. In the in vitro functional assays, crinecerfont inhibited CRF-induced cAMP production in Y79 cells with an IC_{50} value of 3.1nM (1.5 ng/mL), and blocked ACTH secretion in AtT-20 mouse pituitary tumor cells, demonstrating that crinecerfont acts as a functional antagonist of CRF1 receptors ([Figure 1](#)).

Figure 1. Crinecerfont Antagonizes CRF-Induced Pituitary ACTH Secretion (AtT-20 Cells)

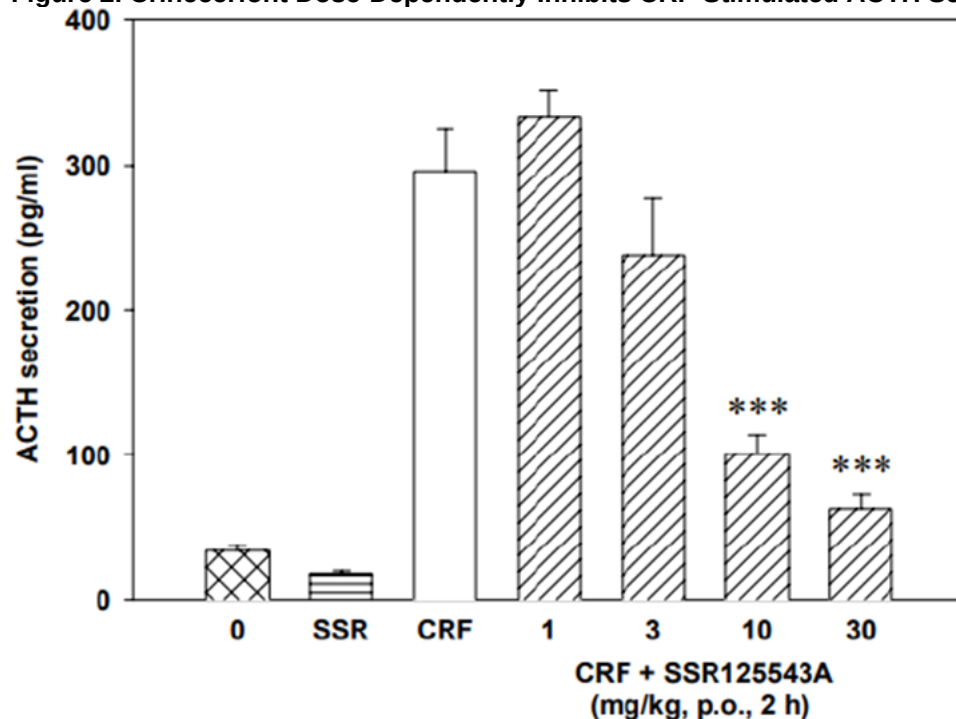


Source: Applicant's NDA submission

Abbreviations: ACTH, adrenocorticotropin hormone; CRF, corticotropin-releasing factor

The in vivo primary pharmacodynamic studies reiterated the findings of the in vitro binding and functional studies. The binding of crinecerfont to pituitary and brain CRF1 receptors was evaluated in crude tissue homogenates from rats administered crinecerfont hydrochloride (HCl) orally (PO) or intraperitoneally. The results demonstrated that crinecerfont binds to CRF1 receptors in pituitary and brain, with higher occupancy of CRF1 receptors in pituitary (67 to 81%) than in brain (13 to 29%) at early timepoints (0.5 to 1 hour postdose). The CRF1 receptor binding of crinecerfont was comparable between pituitary and brain at 2 to 24 hours postdose. In vivo, CRF administration caused an increase in plasma ACTH levels. In studies in rats, administration of crinecerfont PO ([Figure 2](#)), intravenously (IV), or intraperitoneally showed a dose-dependent inhibition of CRF-stimulated ACTH secretion with 50% inhibitory dose of 1.3 to 4.9 mg/kg crinecerfont HCl, further demonstrating the antagonist action of crinecerfont on CRF1 receptors. The CRF1 receptor antagonist effects of crinecerfont were further investigated in a stressed rat model. Stress was induced by restraining rats for 15 minutes, which caused up to a 6-fold increase in ACTH plasma levels. When crinecerfont HCl was administered PO to male rats 1 hour before inducing stress, crinecerfont significantly antagonized the stress-induced ACTH increase at 10 mg/kg but not at 3 mg/kg crinecerfont HCl. Crinecerfont did not significantly affect basal plasma ACTH level when administered PO daily up to 1000 mg/kg in nonstressed rats, indicating that physiological ACTH levels were not affected by crinecerfont, which likely reflects maintenance of endogenous positive and negative feedback signals within the hypothalamus-pituitary-adrenal axis.

Figure 2. Crinecerfont Dose-Dependently Inhibits CRF-Stimulated ACTH Secretion in Rats



Source: Applicant's NDA submission (data source: EVV0033 (Figure (5.2) 2

Note: Data from three to eight rats per group were analyzed by student's t test and are depicted as mean±SEM.

*** p<0.001 versus CRF

Abbreviations: ACTH: adrenocorticotrophic hormone; CRF, corticotropin-releasing factor; SEM, standard error of the mean; SSR, 30 mg/kg crinecerfont hydrochloride; SSR125543A, crinecerfont hydrochloride

In conclusion, the Applicant's in vitro and in vivo nonclinical studies support the proposed mechanism of action for crinecerfont as a CRF1 receptor antagonist that reduces CRF-induced increases in ACTH.

11.2. Clinical Pharmacology / Pharmacokinetics

Table 6. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	Pharmacologic Activity
Established pharmacologic class (EPC)	Corticotropin-releasing factor (CRF) type 1 receptor antagonist
Mechanism of action	Crinecerfont binds to CRF1 receptors and inhibits adrenocorticotrophic hormone (ACTH) secretion from the pituitary, thereby reducing excessive production of adrenal androgens. Crinecerfont has a half-maximal inhibitory concentration (IC ₅₀) of 0.6 to 3.99nM (0.290 to 1.93 ng/mL) for the CRF1 receptor.
Active moieties	Crinecerfont
QT prolongation ⁴	A thorough QTc study shows that crinecerfont did not prolong the QT interval to any clinically relevant extent at a dose 4 times the maximum proposed dose of 100 mg bid.
	General Information
Bioanalysis	Crinecerfont plasma concentrations were assessed in all clinical studies using validated bioanalytical methods. Plasma concentrations for crinecerfont's major metabolites [NBI-756179 (M6), NBI-742939 (M4), NBI-1084059 (M9) and NBI-1084060 (M11)] were quantified in select clinical studies. Crinecerfont and its metabolites were quantified using LC-MS/MS methods.
Healthy volunteers versus patients	No clinically meaningful differences in crinecerfont pharmacokinetics were observed between healthy adult subjects and adult subjects with CAH.

Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	Table 7. Steady-State Exposures for Crinecerfont in Adults and Pediatric Subjects			
	Geometric Mean (CV)			
	Parameter	Trial NBI-74788-CAH3003 (Adult)	Trial NBI-74788-CAH2006 (Pediatrics)	
	AUC _{24,ss} (ng·hr/mL)	Dose: 100 mg bid	72,846 (51%)	Dose 100 mg bid (≥55 kg) 74,693 (48%) Dose 50 mg bid (≥20 to <55 kg) 47,062 (51%)
	C _{max} (ng/mL)		4,231 (46%)	Dose 100 mg bid (≥55 kg) 4,555 (43%) Dose 50 mg bid (≥20 to <55 kg) 2,887 (48%)

Source: Applicant's response to the Information Request sent on 10/2/2024
Steady-state exposure parameters are generated from simulation of 500 subjects based on population pharmacokinetic model and weight band appropriate formulation.
Abbreviations: AUC_{24,ss}, 24-hour area under the concentration-time curve at steady state; bid, twice daily; C_{max}, maximum observed plasma concentration; CV, coefficient of variation expressed as a percentage

⁴ Interdisciplinary review team for cardiac safety studies QT study review filed to NDA 218808 in DARRTS and finalized on August 21, 2024.

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CRENESSITY (crinecerfont) oral capsule and oral solution

Characteristic	Drug Information
Range of effective dose(s) or exposure	- Adults: Based on the phase 2 dose-finding study NBI-74788-2001 in adults with CAH, crinecerfont decreased serum A4 levels in a dose-dependent manner, from 50 mg once daily to 100 mg bid, with maximal A4 reduction observed at 100 mg bid (approximately 60% reduction from baseline). In the phase 3 clinical trial, NBI-74788-CAH3003, the Applicant assessed the 100 mg bid dose and showed similar reduction in A4 levels as seen with the phase 2 dose finding study. - Pediatrics: In Study NBI-74788-2008, adolescents (14 to 16 years) with CAH received a 50 mg bid dose, which was selected to match the exposure seen in adults at 100 mg bid and had similar reduction in serum A4 levels as those in adults with CAH. In the phase 3 clinical trial, CAH2006, 100 mg bid and 50 mg bid were studied in pediatric subjects with CAH ≥ 4 years, weighing ≥ 55 kg and between 20 kg to < 55 kg, respectively.
Maximally tolerated dose or exposure	The maximum tolerated dose was not determined. The highest doses evaluated were a single dose of 800 mg and daily doses of 300 mg daily for 28 days.
Dose proportionality	Following once-daily doses over 14 days, AUC and C_{max} for crinecerfont capsules were dose-proportional between 20 mg and 200 mg. Following a single dose of the solution formulation, crinecerfont AUC and C_{max} were dose-proportional between 25 mg and 100 mg.
Accumulation	The accumulation ratio, based on AUC_{24h} , was 1.44 upon twice-daily dosing.
Time to achieve steady state	Crinecerfont achieves steady state in 7 days.
Bridge between to-be-marketed and clinical trial/study formulations	The to-be-marketed capsule formulation was determined to be bioequivalent to the capsules used in the pivotal phase 3 trials. The to-be-marketed oral solution formulation was used in one of the pivotal phase 3 trials.
Absorption	
Bioavailability	Relative bioavailability (oral solution/oral capsule): GMRs (90% CI): C_{max} : 0.83 (0.67, 1.02) and $AUC_{0-\infty}$: 0.87 (0.71, 1.07) The difference in crinecerfont exposure between oral solution and capsule formulation is not considered clinically relevant.
T_{max}	Oral capsule fed conditions (Study NBI-74788-1736): 5 h (2.0, 10) Oral solution fed conditions (Study NBI-74788-1734): 6.1 h (5.0, 12)

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CRENESSITY (crinecerfont) oral capsule and oral solution

Characteristic	Drug Information																		
Food effect (fed/fasted) Geometric least square mean and 90% CI	Table 8. Crinecerfont 100 mg Soft Gel Capsule (Commercial Formulation) and Crinecerfont 100 mg Oral Solution GMR and 90% CI PK Exposure Parameters Comparing Food Effect <table><tr><th>Study</th><th>Meal Type</th><th>Formulation/ Dose</th><th>AUC GMR (90% CI)</th><th>C_{max} GMR (90% CI)</th><th>T_{max}</th></tr><tr><td>NBI-74788-1736</td><td>High-fat/ high-calorie vs. fasted</td><td>Oral capsule 100 mg</td><td>3.27 (2.87, 3.73)</td><td>4.95 (4.09, 5.98)</td><td>5.0 h vs. 6.0 h</td></tr><tr><td>NBI-74788-1734</td><td>High-fat/ high-calorie vs. fasted</td><td>Oral solution 100 mg</td><td>8.27 (6.22, 10.99)</td><td>8.57 (6.84, 10.74)</td><td>6.5 vs. 6.0</td></tr></table> Source: Compiled from Table 7, p. 29, Study NBI-74788-1734 and Table 12, p. 59, Study NBI-74788-1736 Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum observed plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic; T_{max}, time to reach C_{max} Based on the significant food effect seen with crinecerfont oral solution and capsule formulations, the pivotal phase 3 trials were conducted with crinecerfont dosed with breakfast and dinner. Therefore, for labeling, crinecerfont should be administered with the morning and evening meals.	Study	Meal Type	Formulation/ Dose	AUC GMR (90% CI)	C _{max} GMR (90% CI)	T _{max}	NBI-74788-1736	High-fat/ high-calorie vs. fasted	Oral capsule 100 mg	3.27 (2.87, 3.73)	4.95 (4.09, 5.98)	5.0 h vs. 6.0 h	NBI-74788-1734	High-fat/ high-calorie vs. fasted	Oral solution 100 mg	8.27 (6.22, 10.99)	8.57 (6.84, 10.74)	6.5 vs. 6.0
Study	Meal Type	Formulation/ Dose	AUC GMR (90% CI)	C _{max} GMR (90% CI)	T _{max}														
NBI-74788-1736	High-fat/ high-calorie vs. fasted	Oral capsule 100 mg	3.27 (2.87, 3.73)	4.95 (4.09, 5.98)	5.0 h vs. 6.0 h														
NBI-74788-1734	High-fat/ high-calorie vs. fasted	Oral solution 100 mg	8.27 (6.22, 10.99)	8.57 (6.84, 10.74)	6.5 vs. 6.0														
	Distribution																		
Volume of distribution	The geometric mean (CV%) apparent volume of distribution of crinecerfont is 809 L (35%) for subjects with CAH under fed conditions.																		
Plasma protein binding	Crinecerfont is highly bound to human serum albumin (>99.9%), and the binding is not concentration-dependent. Binding to α1 acid glycoprotein is ≥96.6%.																		
Drug as substrate of transporters	Crinecerfont is not a substrate for transporters P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporting polypeptide (OATP) 1B1, or OATP1B3.																		
	Elimination																		
Mass balance results	Following a single dose of 100 mg crinecerfont, 49.4% of the administered dose was recovered over 37 days due to the long apparent terminal half-life of 19.9 days. Approximately 47.3% of the dose was recovered in feces (2.7% of the dose as the parent drug) and <2% in urine (parent drug undetectable).																		
Clearance	Mean (CV%): 3.45 L/hr (37%)																		
Half-life	Effective half-life ~14 h																		
Metabolic pathway(s)	Based on in vitro studies, crinecerfont is metabolized primarily by CYP3A4 and to a lesser extent, by CYP2B6, with possible minor contribution from CYP2C8 and CYP2C19. An active metabolite, M6, was identified but does not contribute significantly to the pharmacological activity of crinecerfont.																		
Primary excretion pathways (% dose)	Based on the mass balance study: Feces (47.3%) and urine (<2%). For the parent drug, 2.7% was recovered in the feces and amount in the urine was undetectable.																		

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CRENESSITY (crinecerfont) oral capsule and oral solution

Characteristic	Drug Information
	Intrinsic Factors and Specific Populations
Body weight	Population pharmacokinetic analyses indicated that body weight is a significant covariate affecting the pharmacokinetics of crinecerfont. Therefore, body weight-banded dosing was used in the pediatric study to ensure comparable exposures to those of adult subjects across pediatric weight groups (i.e., 100 mg bid for subjects weighing ≥ 55 kg and 50 mg bid for subjects weighing 20 to <55 kg). For pediatric subjects between 10 to <20 kg, crinecerfont dose of 25 mg bid is recommended based on exposure-matching to pediatric subjects between 20 to <55 kg.
Age	No clinically significant differences in the pharmacokinetics of crinecerfont were observed based on age ranging from 5 to 54 years.
Renal impairment	Mass balance study indicates that renal excretion is unlikely to be a major elimination pathway of crinecerfont. Population PK analysis indicates that the median decreases in AUC_{24} with mild and moderate renal impairment relative to normal renal function was 2.7% and 8.4%, respectively. Therefore, dosage adjustment is not needed in patients with mild or moderate renal impairment. Considering the potential impact of severe renal impairment on the pharmacokinetics of crinecerfont, and the lack of clinical experience in these patients, crinecerfont is not recommended in patients with severe renal impairment or end-stage renal disease.
Hepatic impairment	Crinecerfont exposure for subjects with mild, moderate, and severe hepatic impairment decreased by 9%, 15%, and 17%, respectively, for C_{max} and 27%, 34%, and 20%, respectively, for $AUC_{0-\infty}$, relative to subjects with normal hepatic function. The 90% CI values for GMR for C_{max} and AUC for all the hepatic impairment groups included unity as compared to the normal hepatic function group. Therefore, hepatic impairment has no clinically significant effect on crinecerfont pharmacokinetics, and dose adjustment is not needed in patients with hepatic impairment.
	Drug Interaction Liability (Drug as a Precipitant)
Inhibition/induction of metabolism	- Effect of crinecerfont on the pharmacokinetics of CYP3A substrates: Concomitant administration of repeated 100-mg daily doses of crinecerfont increased midazolam (sensitive CYP3A substrate) AUC by 23% (90% CI: 9% to 38%) and did not affect the pharmacokinetics of oral contraceptive (nonsensitive CYP3A substrate, 90% CI of GMR for AUC and C_{max} within 0.80 to 1.25). Therefore, crinecerfont is considered a weak CYP3A inhibitor and is unlikely to significantly increase the systemic exposures of glucocorticoids, which are generally not sensitive CYP3A substrates. - Crinecerfont is unlikely to induce CYP3A, CYP1A2, CYP2C9, CYP2B6 or inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 at clinically relevant doses.
Inhibition/induction of transporter systems	Crinecerfont is not an inhibitor of P-gp, BCRP, BSEP, OATP1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 2, multidrug and toxin extrusion transporter (MATE)1, or MATE2-K.

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CRENESSITY (crinecerfont) oral capsule and oral solution

Characteristic	Drug Information
	Drug Interaction Liability (Drug as an Object)
Inhibition/induction of metabolism	- Effect of CYP3A induction: Concomitant administration of rifampin, a strong inducer of CYP3A4 and moderate inducer of CYP2B6, led to a decrease in crinecerfont C_{max} and AUC by 23% and 62%, respectively. Crinecerfont daily dose should be increased by 2-fold (200 mg bid) when administered with strong CYP3A4 inducers. Crinecerfont dosage should be increased to 200 mg with the evening meal (total daily dose of 300 mg) in patients taking moderate CYP3A4 inducers to ensure adequate efficacy. - Effect of CYP3A inhibition: Concomitant administration of ketoconazole, a strong CYP3A4 inhibitor, resulted in 25% and 45% increases in crinecerfont C_{max} and AUC, respectively. Dose adjustment of crinecerfont is not necessary when used concomitantly with CYP3A4 inhibitors. - Crinecerfont dosage adjustment is not necessary when used in combination with drugs that are inhibitors of CYP2B6, CYP2C9, CYP2C19, CYP1A2, CYP2C8, or CYP2D6.
Inhibition/induction of transporter systems	Crinecerfont is not a substrate for transporters P-gp, BCRP, BSEP, OATP1B1, or OATP1B3.

Source: Clinical pharmacology reviewer-generated based on data from the NDA

Abbreviations: A4, androstenedione; AUC, area under the concentration-time curve; AUC_{24} , AUC from 0 to 24 hours; $AUC_{0-\infty}$, AUC from 0 to infinity; bid, twice daily; CAH, congenital adrenal hyperplasia; C_{max} , maximum observed plasma concentration; CV, coefficient of variation; CYP, cytochrome P450; GMR, geometric mean ratio; LC-MS/MS, liquid chromatography with tandem mass spectrometry; PK, pharmacokinetic; QTc, corrected QT; T_{max} , time to reach C_{max}

12. Efficacy (Evaluation of Benefit)

12.1. Assessment of Dose and Potential Effectiveness

The Applicant has proposed the following crinecerfont dose regimens:

- Adults and pediatric patients weighing ≥ 55 kg: 100 mg twice daily PO with food
- Pediatric patients aged 4 years and older weighing 20 kg to < 55 kg: 50 mg twice daily PO with food
- Pediatric patients aged 4 years and older weighing 10 kg to < 20 kg: 25 mg twice daily PO with food

The proposed dosing regimens for adult patients and pediatric patients weighing ≥ 20 kg are the same as those in Trial CAH3003 (adult trial) and Trial CAH2006 (pediatric trial; see details in Section [12.2](#)). Therefore, the appropriateness of the proposed doses is supported by the safety and efficacy data from these pivotal phase 3 trials. The proposed dosing regimen for pediatric patients weighing 10 to < 20 kg is supported by exposure matching to pediatric subjects weighing 20 to < 55 kg and is considered acceptable (see Section [12.1.3](#)).

12.1.1. Dose Selection Rationale for Pivotal Trials

12.1.1.1. Adult Phase 3 Trial Dose Selection

The dose selection for the phase 3 adult study, Trial CAH3003, was based on the phase 2 study, Trial CAH2001, an open-label, multiple-dose, sequential dose-escalation study to assess the pharmacokinetics, pharmacodynamics, safety, and tolerability of crinecerfont in adult male and female subjects 18 years to 50 years of age with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH. The study assessed four crinecerfont dosing regimens administered for 14 days in a sequential manner. Dose cohorts with sample sizes are listed below:

- Cohort 1 (N=8): 50 mg once daily at bedtime with Ensure Plus® (350 calories, 11 grams total fat, 20 grams sugars, 13 grams protein, and 50 grams carbohydrate)
- Cohort 2 (N=7): 100 mg once daily at bedtime with Ensure Plus
- Cohort 3 (N=8): 100 mg once daily with the evening meal
- Cohort 4 (N=8): 100 mg twice daily at breakfast and dinner

The doses selected for this phase 2 dose-finding study were based on the following data:

- Crinecerfont 50 mg was well tolerated in single- and repeat-dose safety and pharmacokinetic (PK) studies in healthy volunteers.
- Doses up to 200 mg were well tolerated in single-dose and repeat-dose studies in healthy subjects.
- Crinecerfont 100 mg daily was well tolerated in an 8-week double-blind study in adult male and female subjects with major depressive disorder.
- The anticipated steady-state exposures with the selected crinecerfont doses, using the predicted maximum observed plasma concentration (C_{max}) and area under the concentration-time curve (AUC), were within the acceptable safety margins defined by the nonclinical toxicology studies.

Per the Applicant, reductions in ACTH, 17-OHP, and A4 relative to baseline levels were observed in most of the subjects across all dose regimens after receiving 14 days of treatment with crinecerfont. A dose response was observed for androstenedione reduction, with the greatest median reduction observed in the 100 mg twice daily dose group (64%) compared to the other dose groups (21%, 42%, and 51% change from baseline, with 50 mg at bedtime, 100 mg at bedtime, and 100 mg with evening meal, respectively; [Table 9](#)).

In addition, the responder rate (i.e., >50% reduction of A4) was greatest in the crinecerfont 100 mg twice daily (bid) group (75%) compared to responder rates between 50% and 63% for the other dose groups. It should be noted that crinecerfont needs to be administered with food due to low bioavailability under fasting conditions. Various meal types (i.e., Ensure Plus versus breakfast and dinner) were used across the cohorts. Similar crinecerfont drug exposures were observed between cohort 2 (100 mg with Ensure Plus) and cohort 3 (100 mg with evening meal). Therefore, the use of different meal types across treatment arms is unlikely to confound the dose-finding results.

Crinecerfont was generally well tolerated in all four dosing cohorts, and there was no dose relationship in the incidence, type, or severity of adverse events. Therefore, 100 mg twice-daily dosing was selected for the phase 3 adult study, CAH3003. It should be noted that interpretation of the dose response for A4 reduction may be confounded by different baselines of A4 among the four dosing cohorts, between-subject variabilities of this pharmacodynamic marker, and relatively small sample sizes across dose groups (refer to Section [20.2.10](#) for details).

12.1.1.2. Pediatric (Weight > 20 kg) Phase 3 Dose Selection

The dose selection for the phase 3 pediatric trial, CAH2006, was based on the following:

- Clinical benefits observed in the phase 2 study, NBI-74788-CAH2008, an open-label multiple-dose study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of crinecerfont in eight pediatric subjects (14 to 16 years old with mean body weight of 70 kg) with a documented medical diagnosis of classic CAH.
- An exposure-matching approach to the adult 100 mg twice-daily dose using population pharmacokinetic (popPK) analysis for pediatric subjects with CAH.

In the phase 2 study, NBI-74788-CAH2008, pediatric subjects with mean body weight of 70 kg received crinecerfont 50-mg capsules twice daily at breakfast and dinner for 14 consecutive days. Study results indicated that on Day 14, compared to baseline, median A4 levels decreased by 58%, and ACTH and 17-OHP as key secondary endpoints decreased by 57% and 69%, respectively ([Table 9](#)). It is interesting that the degree of A4 reduction appears to be comparable to that in adult subjects, despite the fact that these adolescents received only half the dose the adults received (50 mg bid versus 100 mg bid). Nonetheless, in the phase 3 pediatric study, the Applicant selected the same dose as adults for pediatric subjects with body weight ≥ 55 kg based on the exposure-matching approach rather than relying on the pharmacodynamic (PD) findings.

As body weight is a significant PK covariate, body weight-banded dosing was used in pediatric subjects with varying body weights. Specifically, the population PK model informed the doses selected for the pediatric phase 3 study, Trial CAH2006, (i.e., 100 mg bid for pediatric subjects weighing ≥ 55 kg and 50 mg bid for those weighing 20 to < 55 kg), as these doses in children provide comparable crinecerfont exposures to those of adult subjects across pediatric weight groups. Refer to Sections [20.2.11](#) and [20.5](#) for the in vivo study details and pharmacometrics assessment, respectively.

Table 9. Pharmacokinetic Parameters of Crinecerfont and Percent Change From Baseline in Pharmacodynamic Markers of A4, 17-OHP, ACTH Levels at Day 14, Trials NBI-74788-CAH2001 and NBI-74788-CAH2008

Parameter	Adult Study (NBI-74788-CAH2001)				Pediatric Study (NBI-74788-CAH2008)
	50 mg Once Daily at Bedtime* (n=7)	100 mg Once Daily at Bedtime* (n=7)	100 mg Once Daily With Evening Meal (n=8)	100 mg With Breakfast and Dinner (n=8)	50 mg With Breakfast and Dinner (n=8)
Mean AUC ₂₄ (ng·hr/mL) (SD)	14,300 (3,480)	37,400 (14,100)	34,800 (6300)	66,900 (20,200)	29,339 (15,618)
Mean C _{max} (ng/mL) (SD)	1350 (205)	3510 (1,090)	3810 (1,200)	5590 (2,760)	2,102 (1,543)
% CFB median reduction in A4 level (min, max)	-21.3 (-83.7, 77.5)	-42.2 (-91.8, -14.9)	-50.6 (-85.3, 348.2)	-63.8 (-90.3, -33.3)	-58.27 (-91.4, 52.8)
% CFB median reduction in 17-OHP level (min, max)	-59.8 (-95.0, 2.7)	-58.3 (-96.1, 7.6)	-52.8 (-95.1, 774.4)	-64.3 (-93.9, -7.4)	-69.48 (-90.4, 105.4)
% CFB median reduction in ACTH level (min, max)	-54.2 (-88.8, 26.3)	-62.6 (-91.2, 132.8)	-63.8 (-93.6, 147.6)	-65.8 (-86.3, -29.8)	-57.12 (-80.6, 46.7)

Source: Compiled from Tables 11 (p.60) and 8 (p.52) in NBI-74788-CAH2001; Table 6 in NBI-74788-CAH2008

* Under fed conditions (Ensure Plus); CV%, coefficient of variation expressed as a percentage; PK and PD parameters were obtained at steady state on Day 14 after daily dosing schedule as described above; PD data reflect morning window over 14 days
Abbreviations: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotrophic hormone; AUC, area under the concentration-time curve; C_{max}, maximum observed plasma concentration; max, maximum; min, minimum; CAH, congenital adrenal hyperplasia; CFB, change from baseline; PD, pharmacodynamic; PK, pharmacokinetic

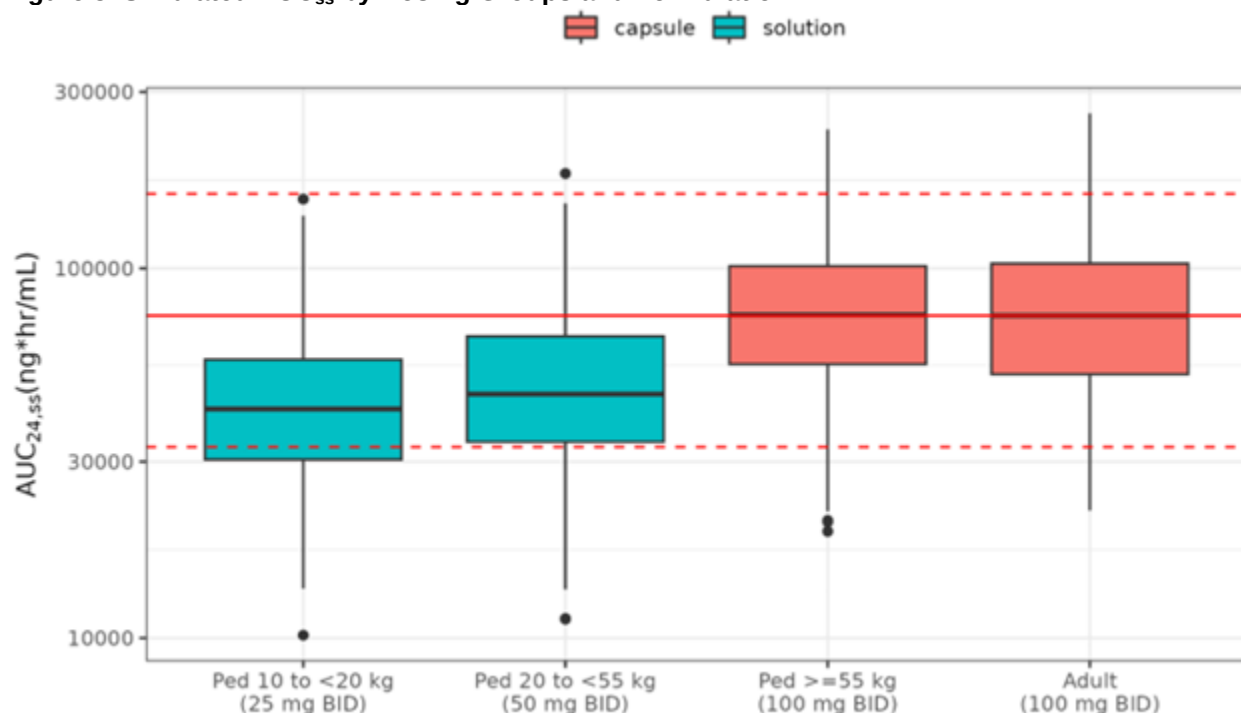
Dose selection is discussed further in Section [12.3.1](#).

12.1.1.3. Dose for Pediatric Patients Weighing 10 to <20 kg

The phase 3 pediatric clinical trial (CAH2006) did not enroll any subjects in the 10 to <20 kg weight band; instead, the Applicant relied upon popPK modeling and exposure matching to support the proposed dosing of 25 mg twice daily in the pediatric subgroup of 10 to <20 kg weight band and down to 4 years of age. The dose for the 10 to <20 kg pediatric subgroup was informed by the dose for pediatric subjects weighing 20 kg to <55 kg. The 20 kg to <55 kg subgroup was chosen as the reference population because of similarities between the two groups with respect to disease state, pathophysiology, disease progression, and expected efficacy response. Furthermore, efficacy was demonstrated at the dose administered to the 20 kg to <55 kg pediatric subgroup, which provided additional support to rely on that subgroup for dose determination for the <20 kg weight group (refer to Section [12.3.1](#)).

Utilizing modeling and simulation in virtual pediatric subjects of 10 to <20 kg and at least 4 years of age, 25 mg twice daily is projected to produce similar exposures (i.e., 24-hour area under the concentration-time curve and 24-hour maximum concentration) to those of the 50 mg twice daily regimen in pediatric subjects of 20 to <55 kg. Additionally, a high proportion of virtual pediatric subjects weighing 10 to <20 kg is expected to have crinecerfont exposures within the model-predicted adult exposure ([Figure 3](#)). Collectively, the proposed dosage of 25 mg twice daily for pediatric patients weighing 10 kg to <20 kg is expected to have similar safety and efficacy based on comparable exposures observed in pediatric subjects weighing 20 kg to <55 kg and in adults (refer to Section [20.5.5](#)).

Figure 3. Simulated AUC_{ss} by Dosing Groups and Formulation



Source: Applicant's popPK report, Figure 1.2, page 19

Dashed red lines represent the 5th and 95th percentiles of the adult 100 mg bid 24-hr AUC at steady-state; solid red line represents the median; box represents the interquartile range (IQR), with the median indicated by the horizontal black line within the box; whiskers represent the range from quartile 1 minus 1.5*IQR to quartile 3 plus 1.5*IQR; outliers are indicated by black points
Abbreviations: AUC_{ss}, area under the concentration-time curve at steady state; bid, twice daily; ped, pediatric; popPK, population pharmacokinetics

12.1.2. Exposure Response

Utilizing the final popPK model and phase 3 clinical data, the Applicant performed exposure-response (E-R) analyses in adults and in pediatric subjects with CAH independently in each population. The efficacy endpoints in the phase 3 clinical trials included the change from baseline in serum A4 prior to morning glucocorticoid dose at Week 4, the percent change from baseline in glucocorticoid daily dose at Week 24 for adults and at Week 28 for pediatric subjects, and the achievement of a reduction in glucocorticoid daily dose to physiologic levels at Week 24 for adults and Week 28 for pediatric subjects while maintaining androgen control. For safety E-R, the most frequent adverse events for adult (i.e., fatigue) and pediatric subjects (i.e., headache) were selected as exploratory safety endpoints for independent analyses in each population.

The E-R efficacy analyses demonstrated that across the studied exposure ranges, for the proposed adult and pediatric dosing regimens (i.e., 100 mg twice daily dose in adults and pediatric subjects weighing ≥ 55 kg; 50 mg twice daily in pediatric subjects weighing 20 to < 55 kg), the E-R efficacy relationships were relatively flat for change from baseline in serum A4 (prior to morning glucocorticoid dose) at Week 4 and percent change from baseline in glucocorticoid daily dose ([Figure 4](#)).

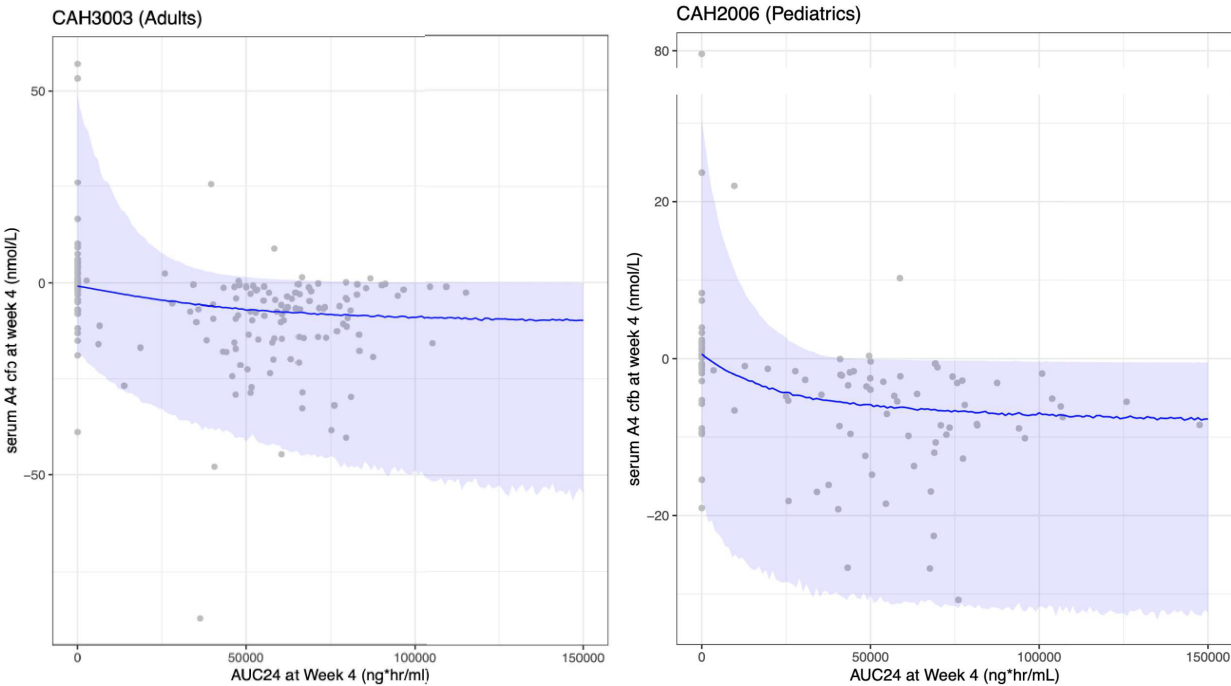
The E-R analyses demonstrated an increase in probability of achieving a reduction in glucocorticoid daily dose to physiologic levels (while maintaining serum A4 control) across studied exposure ranges in the adult and the pediatric E-R models. However, the 95% confidence interval of the slope (i.e., log-odds ratio) for drug exposure contains zero in the pediatric model and is numerically close to zero in the adult model, suggesting that other factors in addition to crinecerfont exposure may be driving the probability of glucocorticoid response.

The following limitations should also be considered when interpreting the E-R findings:

- The exposure ranges in the E-R analysis were relatively narrow. Specifically, the E-R analysis was based on data from the phase 3 trials in adult and pediatric subjects (i.e., Trials CAH3003 and CAH2006). It should be noted that only one dose level was studied in the adult phase 3 trial, data of which was used for the E-R analysis, and pediatric doses were selected to match the adult population.
- An E-R analysis was performed for the most common treatment-emergent adverse event in the adult and pediatric phase 3 trials. There was no apparent relationship between crinecerfont exposure and proportion of adults with fatigue at Week 24 across the studied exposure range. In pediatric subjects, the probability of headache increased across studied exposures at Week 28; however, this finding may have limited interpretation given the small number of pediatric subjects who experienced this adverse event in the crinecerfont arm versus placebo (17 and 2 subjects, respectively).

Overall, the results from the exposure-efficacy and exploratory exposure-safety analyses support the proposed doses for adult and pediatric subjects with CAH (refer to Section [20.5](#) for details on the E-R analyses).

Figure 4. Simulated and Observed Serum A4 Change From Baseline at Week 4 vs. AUC₂₄ at Week 4



Source: Applicant's E-R report, Figures 13.2 and 13.3, pages 97 and 102
Grey points represent the observed data; blue line is the model-predicted median; shaded area, 90% CI
Abbreviations: AUC, area under the concentration-time curve; cfb, change from baseline; E-R, exposure-response

12.1.3. Bioequivalence of Phase 3 Capsule and Commercial Capsule Formulation

Study NBI-74788-1736 demonstrated the bioequivalence between the phase 3 crinecerfont capsules (two 50 mg capsules) and the commercial capsules (one 100 mg capsule) (see [Table 10](#)). A biowaiver was granted for the compositionally proportional capsules at 25 mg and 50 mg.⁵

Table 10. Bioequivalence of Phase 3 Crinecerfont (2×50 mg) Capsule and Commercial Capsule (100 mg) (n=49)

Pharmacokinetic Parameter (Unit)	Treatment Comparison	Geometric LSM Softgel-Fed (test)	Geometric LSM Hardgel-Fed (reference)	Geometric Mean Ratio	90% CI
AUC _{0-tlast} (ng×hr/mL)	Softgel-Fed Versus Hardgel-Fed	67935	67266	1.01	(0.94, 1.09)
AUC _{0-inf} (ng×hr/mL)	Softgel-Fed Versus Hardgel-Fed	72461	73084	0.99	(0.91, 1.08)
C _{max} (ng/mL)	Softgel-Fed Versus Hardgel-Fed	4634	4342	1.07	(0.98, 1.16)

Source: Table 10, p. 48. Study NBI-74788-1736. [Link to CSR 1736](#).
Abbreviations: AUC, area under the concentration-time curve; AUC_{0-inf}, AUC from time 0 to infinity; AUC_{0-tlast}, AUC from time 0 to the time of the last measurable concentration; CI, confidence interval; C_{max}, maximum observed plasma concentration; LSM, least-squares mean

⁵ Biopharmaceutical review of NDA 218808 authored by Dr. Rajesh Sakvur;
<https://panorama.fda.gov/document/view?ID=66db380a002e007d650f644244ac4de7>

12.1.4. Switching Between Oral Solution and Capsule Formulation

Crinecerfont is available as an oral solution and as capsules. Study NBI-74788-1716 compared the crinecerfont exposure between the oral solution and the phase 2 capsule formulation. The results show the two formulations were not bioequivalent and crinecerfont exposure ($C_{\max}$ and AUC) from the oral solution was ~15% less than the phase 2 capsule formulation⁶ (refer to Section 20.2.4). In addition, the popPK analysis indicates that the mean exposure for the oral solution is expected to be 26% lower than that for the capsule formulation (Figure 5).

Nonetheless, the Applicant is proposing that the oral solution and the commercial capsule formulation can be switched based on patient preference.

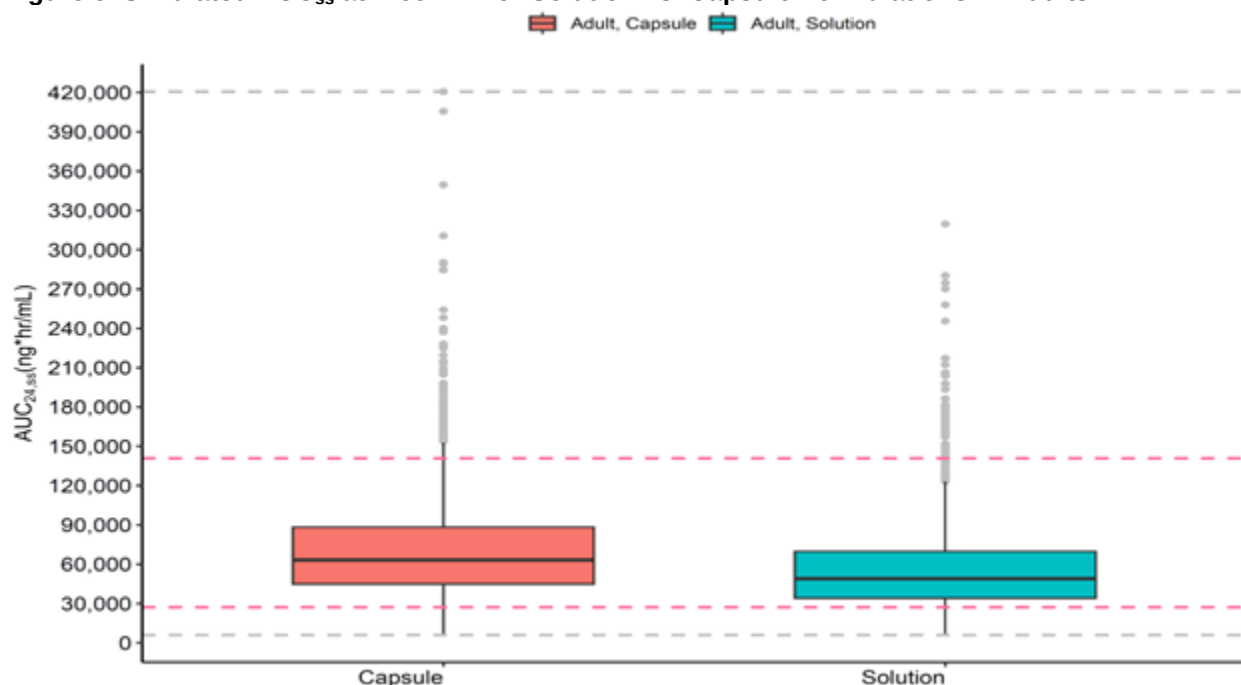
The review team agrees with the Applicant's proposal based on the following considerations:

- This is consistent with the phase 3 pediatric clinical trial (NBI-74788-CAH2006), where subjects were allowed to switch from the oral solution to the capsule formulation in the open-label phase. In clinical practice, we expect the most common scenario to be a switch from oral solution to capsule when pediatric patients become old enough to swallow the capsule. Given that the capsule formulation has slightly higher bioavailability than the oral solution, we do not expect a loss of efficacy when switching to the capsule formulation. In addition, the safety with the capsule formulation has been established in the phase 3 clinical trials.
- Simulation results show that, despite numerically lower exposure (i.e., steady-state AUC) with the oral solution, a large percentage of the simulated exposures in subjects receiving the oral solution fall within those of the capsule formulation.
- The Applicant is proposing the 25 mg bid solution for pediatric patients weighing 10 to <20 kg, and the 50 mg bid solution for pediatric patients weighing 20 to <55 kg. In the randomized, placebo-controlled portion of the pediatric phase 3 trial, about 50% of the subjects were in the 20 to <55 kg weight band (37 crinecerfont, 14 placebo) and received the 50 mg bid (or placebo) solution. The remaining ~50% of subjects were in the ≥55 kg weight band (32 crinecerfont, 20 placebo) and received the capsule. These subgroups achieved similar reductions in glucocorticoid doses. Although the trial did not enroll pediatric subjects weighing <20 kg, the pharmacokinetic exposure with the 25 mg bid solution in the 10 to <20 kg weight band is expected to match that of the 50 mg bid solution in the 20 to <55 kg weight band (see Section 12.3).
- Exposure-efficacy models based on phase 3 clinical data with both oral solution and capsule formulations demonstrate that the E-R relationships are relatively flat across studied exposure for adult and pediatric subjects, respectively.

Based on these considerations, we conclude that the difference in crinecerfont exposure between the oral solution and capsule is not considered clinically meaningful.

⁶ The phase 2 capsule formulation is expected to have a similar crinecerfont exposure to the commercial formulation, as it is nearly identical in composition to the phase 3 capsule formulation, which is bioequivalent to the commercial capsule formulation. The GMRs and 90% CIs for $AUC_{0-\infty}$ and $C_{\max}$ of the commercial capsule compared to the phase 3 capsule at the 100 mg dose were 1.01 (0.94, 1.09), 0.99 (0.91, 1.08), and 1.07 (0.98, 1.16), respectively.

Figure 5. Simulated AUC_{ss} at Week 24 for Solution vs. Capsule Formulations in Adults



Source: Reviewer's analysis

Box represents the interquartile range (IQR) with the median indicated by the horizontal black line within the box; whiskers represent the range from 25th percentile minus 1.5*IQR to 75th percentile plus 1.5 IQR; outliers are indicated by grey points; horizontal dashed grey lines represent minimum to maximum AUCs of the capsule formulation; horizontal dashed red lines represent 5th to 95th percentiles of AUCs of the capsule formulation

Abbreviations: AUC_{ss}, steady-state area under the concentration-time curve

12.2. Clinical Studies/Trials Intended To Demonstrate Efficacy

12.2.1. Results of Pooled Analyses

Not applicable. The two trials were not pooled because the study designs and study populations differed.

12.2.2. Trial CAH3003

12.2.2.1. Design, Trial CAH3003

Overall Design

Trial CAH3003 is titled “A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of crinecerfont in adult subjects with classic congenital adrenal hyperplasia, followed by open-label treatment.” The study design is appropriate to demonstrate efficacy and is depicted in [Figure 6](#).

This phase 3 trial consisted of a 4-week screening period; a 24-week double-blind, placebo-controlled treatment period; a 6-month open-label treatment period; a 6-month open-label or

double-blind, active-controlled treatment period; and an open-label extension. The primary objective was to evaluate the efficacy and safety of oral crinecerfont 100 mg twice daily compared with placebo in reducing daily glucocorticoid dosage while maintaining adrenal androgen control.

24-Week Randomized, Double-Blind, Placebo-Controlled Treatment Period (Day 1 to Week 24)

A total of 182 adult subjects with classic CAH caused by 21-hydroxylase deficiency who required supraphysiologic doses of glucocorticoids to control androgen excess (i.e., glucocorticoid dose >13 mg/m²/day hydrocortisone equivalents) were randomized in a 2:1 ratio (active: placebo) to receive crinecerfont 100 mg taken orally twice daily with breakfast and the evening meal or placebo. The 24-week treatment period consisted of a 4-week glucocorticoid stable dose phase, an 8-week glucocorticoid reduction period, and a 12-week glucocorticoid optimization period.

Week 1 to Week 4

During the first 4 weeks of the study, subjects were maintained on their baseline glucocorticoid regimen.

Week 4 to Week 12

Subjects underwent downward dose-titration of their glucocorticoid dosage to a target of 8 to 10 mg/m²/day hydrocortisone equivalents by Week 12.

Week 12 to Week 24

Glucocorticoid dosage was adjusted if needed based on androstenedione (A4) levels, presence of symptoms of glucocorticoid insufficiency, or hyperandrogenism. The treatment goal was to maintain A4 levels at $\leq 120\%$ of the subject's baseline or upper limit of normal (ULN) for age and sex.

Open-Label Treatment Period (Week 24 to Month 12)

At Week 24 (Month 6), subjects transitioned to a 6-month open-label period during which all subjects received crinecerfont 100 mg twice daily until Month 12. During Months 7 through 10, glucocorticoid dosage was reduced as tolerated if androstenedione levels were controlled (i.e., $\leq 120\%$ of the subject's baseline or $\leq$ ULN for age and sex) to a goal of 8 to 10 mg/m²/day hydrocortisone equivalents by Month 10.

In all parts of the study that allowed for glucocorticoid dose reduction, dose was reduced at a rate of approximately 10% to 20% per month.

Open-Label or Double-Blind Active-Controlled Treatment Period (Month 12 to Month 18)

At Month 12, subjects whose glucocorticoid dosage remained greater than 11 mg/m²/day hydrocortisone equivalents were rerandomized (2:1 ratio) to receive crinecerfont 100 mg every morning and 200 mg every evening, or to continue 100 mg twice daily, in a blinded fashion. Glucocorticoid reduction could be reattempted after the first month of blinded treatment, as

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tolerated, with the goal of achieving a glucocorticoid dose of 8 to 10 mg/m²/day by Month 18 while maintaining control of A4.

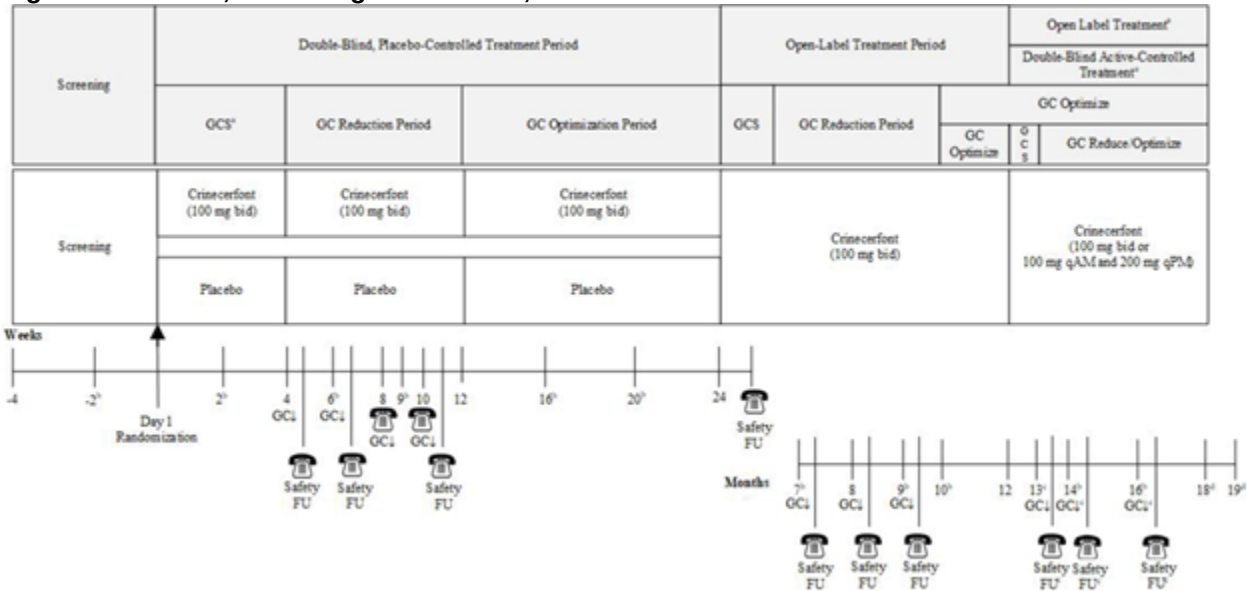
Subjects who had been successfully able to reduce their glucocorticoid dosage to ≤11 mg/m²/day hydrocortisone equivalents continued to receive crinecerfont 100 mg twice daily in an open-label fashion.

Open-Label Extension Period (Month 18 Onward)

After Month 18, subjects could enter an open-label extension period during which they initially received crinecerfont 100 mg bid with adjustment as needed to a maximum crinecerfont dose of 100 mg every morning (qAM) and 200 mg every evening (qPM). Glucocorticoid dose was adjusted as needed to achieve the lowest dose required to maintain adequate disease control. After the Month 24 visit, subjects could consider transitioning to crinecerfont 200 mg qPM.

A final posttreatment visit occurred approximately 1 month after the subject’s final dose of study drug.

Figure 6. Schema, Screening to Month 18, Trial CAH3003



Source: Clinical study report CAH3003, Figure 1, p. 23
a Subjects with GC dose ≤11 mg/m²/day at Month 12 continued to receive OLE treatment. Subjects with GC dose >11 mg/m²/day at Month 12 were rerandomized to one of two active treatment regimens (continue 100 mg bid or 100 mg qAM, 200 mg qPM).
b At home or study site.
c Only for rerandomized subjects.
d Subjects who did not enter the OLE underwent a follow-up visit approximately 28 days after the last dose of study treatment.
Abbreviations: bid, twice daily, FU, follow-up; GC, glucocorticoid; GCS, GC stable period; OLE, open-label extension

During the study, subjects returned to the study clinic at regular intervals for efficacy and safety assessments. The complete schedule of assessments during all trial periods is shown in Section 21.

Efficacy Endpoints

The primary efficacy endpoint was the percent change from baseline in glucocorticoid (GC) daily dose (in hydrocortisone equivalents adjusted for body surface area [BSA] in mg/m²/day) at

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Week 24 while also achieving Week 24 androstenedione levels in the controlled range (i.e., $\leq 120\%$ of baseline or $\leq \text{ULN}$ for age and sex).

Glucocorticoid daily dose was calculated at baseline and at Week 24. If glucocorticoid dosing alternated over the course of 2 consecutive days, then the average of the glucocorticoid dose on those days was used to calculate the glucocorticoid daily dose. If glucocorticoid dosing alternated between weekdays and weekends (or another weekly regimen that varied by day of the week), then the average daily dose was calculated as the sum of the glucocorticoid doses over the 7-day period divided by 7.

According to the statistical analysis plan, the androstenedione level prior to morning glucocorticoid dose served as the baseline and Week 24 level. If androstenedione levels prior to morning glucocorticoid were not available, then androstenedione levels after morning glucocorticoid dose were used.

Subjects who had a decrease in glucocorticoid daily dose but did not meet the definition of androstenedione control at Week 24 were considered to have a zero percent change from baseline in the glucocorticoid daily dose at Week 24.

Key secondary efficacy endpoints were the following:

- Change from baseline in serum androstenedione at Week 4 (while glucocorticoid dose was stable)
- Achievement of a reduction in glucocorticoid daily dose to $\leq 11 \text{ mg/m}^2/\text{day}$ hydrocortisone equivalents at Week 24 (while Week 24 androstenedione was adequately controlled)
- Change from baseline in homeostatic model assessment of insulin resistance (HOMA-IR; in fasting subjects not on insulin, at Week 24)
- Percent change from baseline in weight at Week 24
- Change from baseline in percent total fat mass at Week 24

The study design was adequate to meet its stated objectives. The data from Trial CAH3003 that were submitted with the NDA are results from the 24-week (i.e., Weeks 0 to 24) randomized, double-blind, placebo-controlled treatment period and the open-label treatment period, which capture treatment Week 24 through Month 12 (data cutoff of July 19, 2023). The 120-day Safety Update included new data obtained in the open-label extension treatment period from Month 12 through the data cutoff of January 16, 2024. The trial is ongoing.

The efficacy analysis is based primarily on data obtained during the initial 24-week placebo-controlled treatment phase.

12.2.2.2. Eligibility Criteria, Trial CAH3003

The eligibility criteria are reflective of the patient population who would benefit from a reduction in glucocorticoid dose. Study subjects were required to be taking supraphysiologic glucocorticoid doses (total daily dosage $> 13 \text{ mg/m}^2/\text{day}$ in hydrocortisone dose equivalents).

The study enrolled adult male and nonpregnant, nonlactating female subjects aged 18 years and older with a diagnosis of classic 21-hydroxylase deficiency CAH (accepted diagnostic criteria were an elevated 17-hydroxyprogesterone level, confirmed cytochrome P450 (CYP) 21A2

genotype, positive newborn screening with confirmatory second-tier testing, or cosyntropin stimulation testing). Individuals with other forms of classic CAH were excluded.

Subjects were also required to be on a stable supraphysiologic glucocorticoid dose regimen (defined as >13 mg/m²/day in hydrocortisone dose equivalents; prior to protocol Amendment 5, the threshold was >14 mg/m²/day) and consisting of one or more of the following orally administered glucocorticoids: hydrocortisone, prednisone, prednisolone, methylprednisolone, or dexamethasone.

If treated with fludrocortisone for salt wasting, the dosage was stable for at least 1 month prior to screening, with an upright plasma renin activity (PRA) during screening that was not greater than ULN while maintaining a usual sodium intake. If PRA was $>ULN$, the subject must have systolic blood pressure >100 mm Hg, without orthostatic hypotension, and with serum sodium and potassium in the normal range.

Additional exclusions were conditions requiring chronic glucocorticoid therapy at systemic exposures that may interfere with study endpoints; increased risk of adrenal crisis; history of malignancy; laboratory findings consistent with impaired hepatic or renal function; anemia, thrombocytopenia, neutropenia (absolute neutrophil count [ANC] $<1.0 \times 10^3/\text{mm}^3$), or impaired coagulation; and active suicidal ideation in the 6 months prior to screening or any history of suicidal behavior within the past year based on the Columbia-Suicide Severity Rating Scale collected at screening.

Contraception was required in female subjects of childbearing potential with fertile male partners from screening until the final study visit or 30 days after the last dose of study drug, whichever was longer.

Medications prohibited during the trial were:

- Orally administered glucocorticoids for indications other than CAH
- Strong inducers of CYP3A4 or CYP2B6 except topically administered medications
- Medications that affect cortisol or glucocorticoid metabolism (e.g., phenytoin, mitotane, phenobarbital, strong CYP3A4 inhibitors) except topically administered medications
- Aromatase inhibitors (e.g., anastrozole, letrozole, testolactone)

12.2.2.3. Statistical Analysis Plan, Trial CAH3003

The full analysis set (FAS), defined as all randomized subjects regardless of adherence to study treatment administration, was used for all efficacy analyses. Continuous efficacy endpoints were analyzed using an analysis of covariance (ANCOVA) model assuming equal variance between the placebo and the treatment group. The ANCOVA model included respective baseline measurement as a covariate and stratification factors and treatment group (crinecerfont 100 mg bid or placebo) as factors. Categorical efficacy endpoints were analyzed using the Cochran-Mantel-Haenszel (CMH) test. The CMH test compared treatment groups (crinecerfont 100 mg bid versus placebo) and included the stratification factors used in the randomization.

The protocol prespecified testing procedure described below was used to control the familywise Type I error rate for the primary and key secondary endpoints ([Figure 7](#)). All significance levels noted below were two-sided.

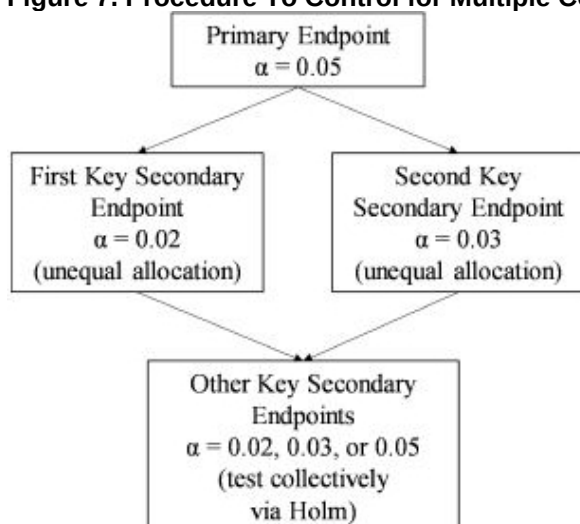
- The primary endpoint was tested using a significance level of 0.05.
- If the primary endpoint was statistically significant, then the first two key secondary endpoints were tested using an unequal allocation of significance levels. The change from baseline at Week 4 in androstenedione was tested using a significance level of 0.02. The achievement of a reduction in glucocorticoid daily dose to physiologic levels (≤ 11 mg/m²/day hydrocortisone equivalent adjusted for BSA) with androstenedione control (as defined for the primary endpoint) was tested using a significance level of 0.03.
- The significance level for the family of the remaining three key secondary endpoints was dependent on whether the first two key secondary endpoints were statistically significant. If both were statistically significant, then the significance level for this family of endpoints was 0.05. If only one was statistically significant, then the significance level for that endpoint was used for this family of endpoints. If neither was significant, then this family of endpoints will not be tested for statistical significance.

Missing Data Handling

The primary efficacy endpoint requires the availability of both the glucocorticoid dose at Week 24 as well as androstenedione values used in the assessment of androstenedione control. The missing data corresponding to the subjects with a missing glucocorticoid dose, androstenedione, or both at Week 24 were multiply imputed as follows:

- For subjects who were on study drug at Week 24 and had missing one or both components of the primary endpoint, their missing Week 24 data were imputed from Week 24 Completers (subjects who completed through the time of the endpoint on study drug) within the same treatment group.
- For subjects who were off study drug at Week 24 and had missing one or both components of the primary endpoint, their missing Week 24 data were imputed from subjects who were classified as “retrieved dropouts” (subjects in the FAS who discontinued study drug but remained in the study and had an evaluable measurement). If there were five or fewer retrieved dropouts, the missing endpoint values would be imputed from subjects in the placebo treatment group. For subjects in the placebo treatment group, missing data were imputed using nonmissing data from subjects in the placebo treatment group.

Figure 7. Procedure To Control for Multiple Comparisons



Source: Statistical analysis plan version 3, page 45

12.2.2.4. Results of Analyses, Trial CAH3003

12.2.2.4.1. Disposition, Baseline Demographics, and Baseline Clinical Characteristics

Disposition During Double-Blind Treatment Period (Baseline to Week 24)

A total of 182 subjects were randomized (122 crinecerfont; 60 placebo). All subjects were included in the FAS. One subject (1.7%) in the placebo group was not dosed and was excluded from the double-blind period safety analysis set. The double-blind period safety analysis set includes all randomized subjects who took at least one dose of study treatment in the double-blind, placebo-controlled period. Most subjects (95.9% crinecerfont; 95.0% placebo) completed the double-blind period and completed study treatment in this period ([Table 11](#)). Reasons for study discontinuation (and study treatment discontinuation) before Week 24 were withdrawal by subject (2.5% crinecerfont; 3.3% placebo), lost to follow-up (0.8% crinecerfont; 1.7% placebo), and an adverse event (AE) (0.8% crinecerfont; 0% placebo).

Table 11. Subject Disposition, All Randomized Subjects

Disposition Category	Placebo (N=60) n (%)	Crinecerfont 100 mg bid (N=122) n (%)	All Subjects (N=182) n (%)
Received study drug	59 (98.3)	122 (100)	181 (99.5)
Completed study drug through Week 24	57 (95.0)	117 (95.9)	174 (95.6)
Completed study through Week 24	57 (95.0)	117 (95.9)	174 (95.6)
Discontinued study and study drug prior to Week 24	3 (5.0)	5 (4.1)	8 (4.4)
Withdrawal by subject	2 (3.3)	3 (2.5)	5 (2.7)
Lost to follow-up	1 (1.7)	1 (0.8)	2 (1.1)
Adverse event	0	1 (0.8)	1 (0.5)

Source: ADSL dataset for Trial CAH3003, statistical reviewer's analysis

Note: Two subjects (One in the placebo treatment group and one in the crinecerfont 100 mg bid treatment group) completed through Week 24 of the study and discontinued at Week 24 but are counted in the "Discontinued Study prior to Week 24" category per data collected on the disposition.

Abbreviation: N, number of subjects; bid, twice daily

Disposition During Open-Label Treatment Period (Weeks 24 to 48)

Of the 182 randomized subjects, 174 (96%) completed the double-blind treatment period. All 174 entered the open-label treatment period (117 crinecerfont; 57 placebo) and were treated with open-label crinecerfont 100 mg bid starting at Week 24. As of the data cutoff date (July 19, 2023), 45% (39% placebo/crinecerfont; 49% crinecerfont/crinecerfont) had completed the study through Month 12 and are included in the efficacy analysis. Data from subjects who had not yet completed the open-label treatment period through Month 12 as of the data cutoff date are not included in the efficacy analyses but are included in the safety analyses. The remainder of the subjects who entered the open-label treatment period completed treatment after the data cutoff date.

Disposition During the Open-Label Extension (Month 12 Onward)

Of the 174 subjects who started the open-label treatment period, 167 (96%) completed open-label treatment through Month 12. All of the 167 who completed the open-label treatment period continued into the open-label extension, 50 of whom were rerandomized at Month 12 and entered the double-blind active-controlled treatment period (Month 12 to Month 18). Their data are not included in the safety analysis. Data from the remaining 117 subjects who were not rerandomized are included in the safety analysis.

Baseline Demographics and Clinical Characteristics

Demographics were generally similar between the treatment groups ([Table 12](#)). The mean age of randomized subjects was 31.3 years (range: 18 to 54 years) in the crinecerfont group and 29.8 years (range: 18 to 58 years) in the placebo group. All subjects were younger than age 65 years. The percentage of male and female subjects was approximately 50% in both treatment groups. Most subjects were White (90.1%) and not Hispanic or Latino (92.3%). Geographic region was the United States for 37.9% of subjects and outside the United States for 62.1% of subjects.

Baseline disease characteristics were generally similar between the treatment group and the placebo group ([Table 13](#)). Participants, on average, were taking supraphysiologic glucocorticoid dosages and had mean androstenedione and 17-hydroxyprogesterone levels significantly above

the clinical guideline-specified goal ranges (androstenedione within the reference range for age and sex and 17-hydroxyprogesterone in the upper normal reference range to mildly elevated ([Speiser et al. 2018](#)). A target 17-hydroxyprogesterone level of less than approximately 1200 ng/dL has been suggested, although target levels are individualized in clinical practice ([Merke 2008](#)).

The mean glucocorticoid total daily dose in hydrocortisone equivalents was 17.6 mg/m²/day (absolute dose 32 mg/day). In adults, a daily absolute hydrocortisone dose of 15 to 25 mg is widely accepted clinically as physiologic replacement ([Bornstein et al. 2016](#); [Husebye et al. 2021](#)). For a typical adult with a body surface area of 1.8 m², this absolute dose translates to 8 to 14 mg/m²/day.

The mean androstenedione level was 619 ng/dL prior to the morning glucocorticoid dose (approximately 3 to 4× treatment goal of A4 level below the upper limit of normal) and 349 ng/dL after the morning dose. The androstenedione reference range for males aged 15 to 60 years is about 15 to 150 ng/dL. For females aged 15 to 60 years, the androstenedione reference range is about 40 to 260 ng/dL.

The mean 17-hydroxyprogesterone level was 9467 ng/dL (about 8× treatment goal of 17-OHP values less than approximately 1200 ng/dL) prior to the morning glucocorticoid dose and 3299 ng/dL after the morning dose. The 17-hydroxyprogesterone reference range for adult males is about 30 to 200 ng/dL. For adult females, the 17-hydroxyprogesterone reference range is about 15 to 70 ng/dL in the follicular phase and 35 to 290 ng/dL in the luteal phase.

Table 12. Subject Demographics, Full Analysis Set, Trial NBI-74788-CAH3003

Characteristic	Placebo (N=60)	Crinecerfont 100 mg bid (N=122)	All Subjects (N=182)
Age (years)			
n	60	122	182
Mean	29.8	31.3	30.8
SD	10.17	9.82	9.93
Median	29.5	29.5	29.5
Min, max	18, 58	18, 54	18, 58
Age category (years), n (%)			
18-25	27 (45.0)	40 (32.8)	67 (36.8)
26-35	21 (35.0)	43 (35.2)	64 (35.2)
≥36	12 (20.0)	39 (31.9)	51 (28.0)
Sex, n (%)			
Male	31 (51.7)	61 (50.0)	92 (50.5)
Female	29 (48.3)	61 (50.0)	90 (49.5)
Ethnicity, n (%)			
Hispanic or Latino	8 (13.3)	6 (4.9)	14 (7.7)
Not Hispanic or Latino	52 (86.7)	116 (95.1)	168 (92.3)
Race, n (%)			
American Indian or Alaska Native	0	1 (0.8)	1 (0.5)
Asian	0	5 (4.1)	5 (2.7)
Black or African American	0	2 (1.6)	2 (1.1)
White	57 (95.0)	107 (87.7)	164 (90.1)
Other	1 (1.7)	2 (1.6)	3 (1.6)
Multiple	1 (1.7)	1 (0.8)	2 (1.1)

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Characteristic	Placebo (N=60)	Crinecerfont 100 mg bid (N=122)	All Subjects (N=182)
Region, n (%)			
United States	21 (35.0)	48 (39.3)	69 (37.9)
Outside United States	39 (65.0)	74 (60.7)	113 (62.1)

Source: ADSL data and Statistical Reviewer's analysis

Percentages are based on the number of subjects in the full analysis set (N).

Abbreviations: bid, twice daily; SD, standard deviation; min, minimum; max, maximum

Table 13. Baseline Disease Characteristics, Full Analysis Set

Characteristic	Placebo (N=60)	Crinecerfont 100 mg bid (N=122)	All Subjects (N=182)
Daily glucocorticoid dose (mg/day; in hydrocortisone equivalents)			
Mean	32.1	32.4	32.3
Median (min, max)	30.0 (20.0, 80.0)	30.0 (20.0, 80.0)	30.0 (20.0, 80.0)
Glucocorticoid (GC) type, n (%)			
Hydrocortisone alone	35 (58.3)	71 (58.2)	106 (58.2)
Prednisone, prednisolone, methylprednisolone, with or without hydrocortisone	19 (32)	34 (28)	53 (29.1)
Dexamethasone, with or without another glucocorticoid	6 (10.0)	17 (14)	23 (12.6)
N (%) taking fludrocortisone at baseline	50 (83)	107 (88)	157 (86)
Disease Markers			
Serum androstenedione (ng/dL) (pre-AM GC dose)			
Mean	587	635	619
Median (min, max)	369 (16, 2364)	417 (41, 5815)	369 (16, 5815)
Serum androstenedione (ng/dL) (post-AM GC dose)			
Mean	370.1	338.0	348.6
Median (min, max)	205.0 (6.0, 1973.0)	206.0 (22.0, 2491.0)	206.0 (6.0, 2491.0)
Daily GC dose (mg/day) in hydrocortisone equivalents			
Median (min, max)	30 (20, 80)	20 (20, 80)	
Daily glucocorticoid dose adjusted for BSA (mg/m ² /day) in hydrocortisone equivalents			
Mean	17.9	17.5	17.6
Median (min, max)	16.5 (13, 39)	15.8 (13, 44)	16.1 (13, 49)
17-OHP ng/dL pre-AM GC dose			
Mean	9787	9314	9467
Median (min, max)	6295 (53, 44466)	7507 (92, 49299)	7207 (53, 49299)
17-OHP ng/dL post-AM GC dose			
Mean	3696	3091	3299
Median (min, max)	1677 (32, 31087)	1882 (21, 33520)	1864 (21, 33520)
Median (min, max) serum androstenedione (ng/dL) (pre-AM GC dose)	363 (16, 2364)	392 (41, 5815)	
Median (min, max) 17-OHP pre-AM GC dose	191 (2, 1347)	223 (3, 1494)	

Source: ADSL data and Statistical Reviewer's analysis

Baseline was defined as the last value before study treatment dosing on Day 1.

Abbreviations: 17-OHP, 17-hydroxyprogesterone; AM, morning; bid, twice daily; BSA, body surface area; GC, glucocorticoid; max, maximum; min, minimum

12.2.2.4.2. Efficacy Results

Efficacy results for Trial CAH3003 include analysis of the completed double-blind period (Day 1 to Week 24) and an interim analysis of the available data for the ongoing open-label period (Week 24 to Month 12) at the data cutoff (July 19, 2023).

12.2.2.4.2.1. Primary Analysis

For the primary efficacy endpoint, the least-squares (LS) mean percent change from baseline in glucocorticoid daily dose at Week 24, while Week 24 androstenedione was controlled at $\leq 120\%$ of baseline or $\leq \text{ULN}$ for age and sex, was -27.3% (standard deviation [SD] 2.4) for the crinecerfont group and -10.3% (SD 3.2) for the placebo group, with an LS mean difference (crinecerfont - placebo) of -17.0% (95% confidence interval [CI]: $-23.8, -10.2$; $p < 0.0001$) (Table 14). For the primary analysis of the primary endpoint, subjects who did not achieve androstenedione control were assigned a change in glucocorticoid dose of 0% .

Table 14. ANCOVA Analysis of Percent Change From Baseline at Week 24, Full Analysis Set

Parameter	Placebo	Crinecerfont 100 mg
N	60	122
Baseline, mean (SD)	17.9 (5.5)	17.5 (4.5)
LSM percent change from baseline (SE)	-10.3 (3.25)	-27.3 (2.42)
Difference in LSM (95% CI) ^a		-17.0 (-23.8, -10.2)
p-value		<0.0001

Source: ADGCM, ADSL data and statistical reviewer's analysis

^a Difference is crinecerfont minus placebo.

- Least-squares (LS) mean based on the ANCOVA model which includes baseline GC dose as a covariate, and treatment group and stratification factors as fixed effects. Summary statistics are based on observed data and ANCOVA analysis results are based on multiply imputed data.

Abbreviations: ANCOVA, analysis of covariance; GC, glucocorticoid; LSM, least-squares mean; SD, standard deviation; SE, standard error

For the primary endpoint, most subjects received study drug and had observed data (93.3% crinecerfont and 95.9% placebo) (Table 15). Overall missing primary endpoint data were minimal (3.8%). Since there were not enough retrieved dropouts, the missing endpoint values were multiply imputed for the primary analyses using data from subjects in the placebo treatment group.

Table 15. Summary of Missing Primary Endpoint at Week 24, Full Analysis Set

Subject Type	Placebo (N=60) n (%)	Crinecerfont 100 mg bid (N=122) n (%)	All Subjects (N=182) n (%)
Completers	56 (93.3)	117 (95.9)	173 (95.1)
Retrieved dropouts	1 (1.7)	1 (0.8)	2 (1.1)
Non-retrieved dropouts	2 (3.3)	4 (3.3)	6 (3.3)
On-drug missing endpoint	1 (1.7)	0	1 (0.5)

Source: Statistical Reviewer's analysis

Abbreviation: bid, twice daily

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A sensitivity analysis was performed to test the equality of variances between the placebo and treatment group. Based on the Bartlett's χ^2 statistic=0.34517 with p-value=0.56, there was not enough evidence (at 0.05 significance level) found against the equal variance assumption. Also, the least squares mean treatment difference (95% CI) obtained from the ANCOVA model adjusted for unequal variances was -17.0 (-23.7, -10.4) is almost identical to what was observed in the primary analysis in [Table 14](#).

A two-way tipping point sensitivity analysis was performed to assess the robustness of the primary efficacy analysis. The significance at $p < 0.05$ was maintained for the primary endpoint when the delta shift for the multiply imputed values was up to 25 mg/m²/day for crinecerfont or up to -25 mg/m²/day for placebo. [Table 16](#) contains all combinations of delta values that tipped the result from statistically significant to not statistically significant. The tipping point ($p \geq 0.05$) was reached when the combined delta shift was 43 mg/m²/day or greater (for example 23 mg/m²/day for crinecerfont and -20 mg/m²/day for placebo). These very extreme values for the tipping point are supportive of the primary results.

Table 16. P-Value for Two-Way Tipping Point Sensitivity Analysis of Primary Endpoint, Full Analysis Set

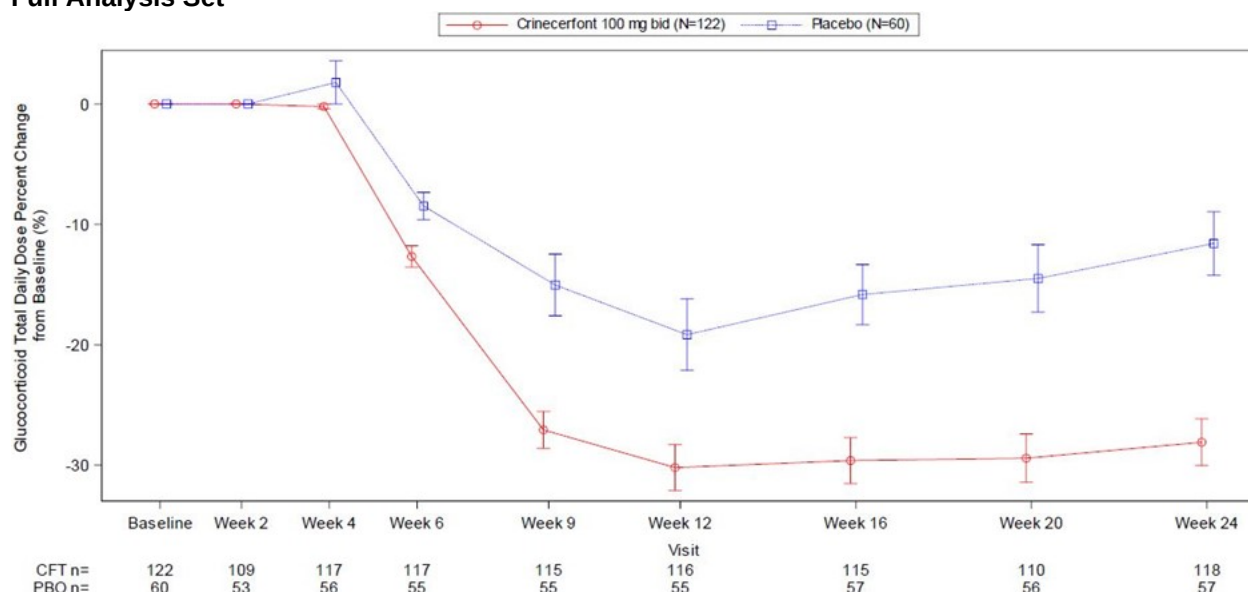
Delta Adjustment for Placebo	Delta Adjustment for Crinecerfont 100 mg bid						
	0	20	21	22	23	24	25
0	<0.0001	0.0036	0.0049	0.0065	0.0086	0.0111	0.0142
-20	0.0007	0.0319	0.0378	0.0445	0.0520	0.0603	0.0696
-21	0.0009	0.0354	0.0417	0.0488	0.0567	0.0654	0.0751
-22	0.0012	0.0393	0.0460	0.0534	0.0617	0.0709	0.0809
-23	0.0016	0.0435	0.0505	0.0584	0.0671	0.0766	0.0870
-24	0.0020	0.0480	0.0555	0.0637	0.0728	0.0828	0.0935
-25	0.0026	0.0529	0.0608	0.0694	0.0789	0.0892	0.1004

Source: ADGC, ADGCM data and statistical reviewer's analysis

Abbreviation: bid, twice daily

[Figure 8](#) shows the mean (standard error) percent changes from baseline in glucocorticoid total daily dose (set to zero for subjects with loss of androstenedione control) by visit. The mean glucocorticoid dose increased toward baseline in the placebo group and was still trending up by Week 24, whereas the mean glucocorticoid dose was maintained at a reduced dose relative to baseline in the crinecerfont group.

Figure 8. Mean ($\pm$ SE) Percent Change From Baseline of Glucocorticoid Total Daily Dose by Visit, Full Analysis Set



Source: ADGC, ADSL and statistical reviewer's analysis

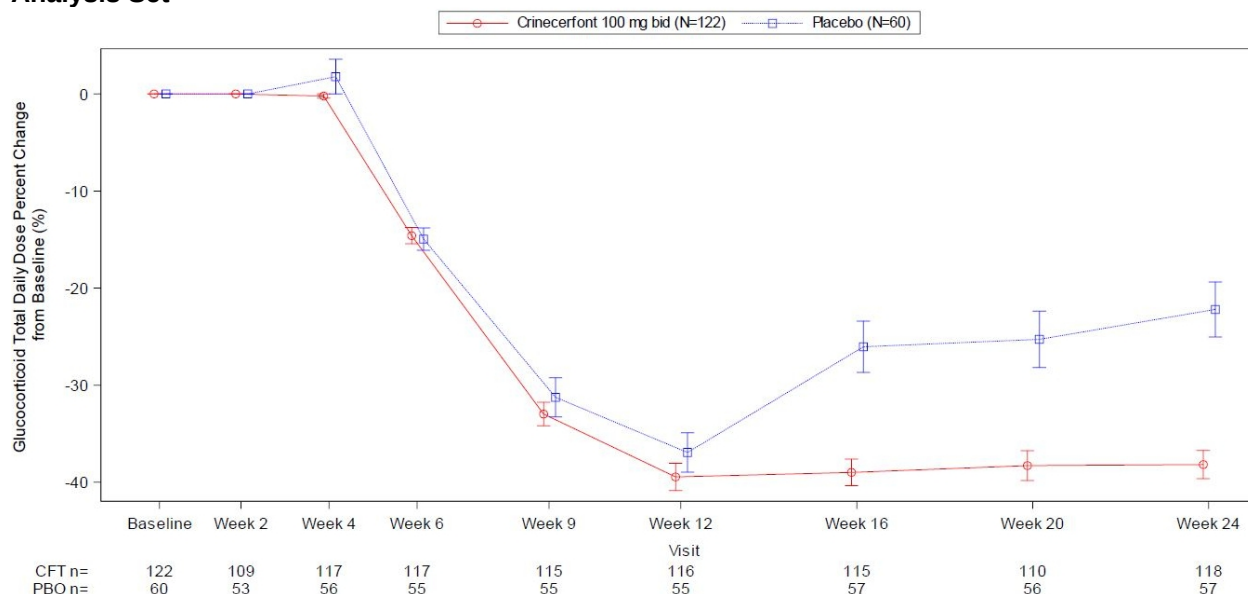
Androstenedione control is defined as androstenedione $\leq 120\%$ of baseline or $\leq$ ULN for age and sex. Subjects not meeting the androstenedione control criteria, had their glucocorticoid daily dose percent change from baseline values set to 0 at each visit where control was not met.

Abbreviations: bid, twice daily; CFT, crinecerfont 100 mg bid; PBO, placebo; SE, standard error; ULN, upper limit of normal

There were 57 subjects (27 in the placebo group and 30 in the crinecerfont treatment group) who did not achieve androstenedione control by Week 24. In the primary analysis, if a subject did not meet androstenedione control criteria, the change (and percentage change) in glucocorticoid daily dose from baseline was set to zero at each visit where control was not met. As an exploratory analysis, the primary analysis was repeated without setting the change in glucocorticoid daily dose to zero for subjects with loss of androstenedione control. In this analysis, the least squares mean treatment difference (-16.3, 95% CI [-22.5, -10.1]) at Week 24 was consistent with that of the primary efficacy analysis. [Figure 9](#) below summarizes the findings of this exploratory analysis at each visit.

Another sensitivity analysis of the primary endpoint was done where the percentage changes in glucocorticoid daily dose for the 57 subjects who did not achieve androstenedione control by Week 24 were replaced with the worst percentage change among all the subjects. Results from this analysis were also consistent (treatment difference of -20.75 with 95% CI [-29.25, -12.26]) with that of the primary efficacy analysis.

Figure 9. Mean ($\pm$ SE) Percent Change From Baseline in Glucocorticoid Total Daily Dose (Without Setting Percent Change as 0 for Subjects With Loss of Androstenedione Control) by Visit, Full Analysis Set



Source: ADGC, ADSL and statistical reviewer's analysis

Androstenedione control is defined as androstenedione $\leq 120\%$ of baseline or $\leq$ ULN for age and sex.

Abbreviations: bid, twice daily; ULN, upper limit of normal; CFT, crinecerfont 100 mg bid; PBO, placebo; SE, standard error

Given the mean baseline glucocorticoid daily dose of 17.6 mg/m²/day hydrocortisone equivalents (absolute dose of 32.3 mg hydrocortisone equivalents) in all study subjects, a mean decrease of 17% (placebo-subtracted difference in the primary analysis of the primary endpoint) would correspond to a mean dose of 14.6 mg/m²/day (absolute mean dose of 26.8 mg/day), for an absolute mean decrease of 3 mg/m²/day (mean decrease of 5.5 mg) hydrocortisone equivalents.

A decrease of 2 to 3 mg/m²/day (about 3.5 to 5.5 mg/day) hydrocortisone equivalents in subjects with CAH treated with supraphysiologic glucocorticoid dosages is clinically meaningful. Published studies show a high prevalence of adverse effects on body weight and bone health in individuals with classic CAH treated with supraphysiologic glucocorticoid dosages. Studies in individuals requiring replacement glucocorticoid therapy show improvements in body mass index, metabolic parameters, and quality of life when supraphysiologic glucocorticoid is decreased to more physiologic levels. In adults, a daily absolute hydrocortisone dose of 15 to 25 mg is widely accepted clinically as physiologic replacement ([Bornstein et al. 2016](#); [Husebye et al. 2021](#)). For a typical adult with a body surface area of 1.8 m², this absolute dose translates to 8 to 14 mg/m²/day.

In published cohort studies, adults and children with classic CAH have a relatively high prevalence of obesity, and adults also have a high prevalence of low bone density. In a cohort of 139 pediatric patients and 44 adults with classic CAH and mean glucocorticoid daily dose in hydrocortisone equivalents of 17.9 mg/m²/day in adults and 15 mg/m²/day in children (similar to the study populations), the prevalence of obesity was 33% in adults and 35% in children. Furthermore, obesity was associated with higher glucocorticoid dose ([Finkelstein et al. 2012](#)).

In a cohort of 165 adults with classic CAH in the United Kingdom, a mean age of 33 years in women and 32 years in men, and median daily dosages of hydrocortisone (25 mg in males, 20 mg in females), prednisone (7.5 mg in males, 6 mg in females), and dexamethasone (0.5 mg

in males, 0.375 mg in females), the prevalence of obesity was 37% in men and 52% in women. In the same study, prevalence of osteopenia and osteoporosis at the lumbar spine for those with available data was 39.2% and 6.8%, respectively.

In a study of adults with primary adrenal insufficiency caused by Addison's disease, decreasing the absolute glucocorticoid dose by 5 mg/day hydrocortisone equivalents and switching from immediate-release to dual-release glucocorticoids for 6 months led to statistically significant improvements in body mass index, hemoglobin A1c, lipid levels, and quality of life ([Delle Cese et al. 2020](#)).

Below we further explore the impact of the changes in glucocorticoid dose on other endpoints in the trial and also assess the proportion of subjects who were able to achieve physiologic-range glucocorticoid doses in the setting of androgen control.

Secondary Efficacy Endpoint Results

The primary analyses of the five key secondary endpoints are given in [Table 17](#). The LS mean change from baseline in serum androstenedione at Week 4 was -299 (37.7) ng/dL for the crinecerfont group, compared with an increase of 46 (51.0) ng/dL for the placebo group. The LS mean treatment difference (crinecerfont - placebo) of -345 ng/dL (95% CI: -457, -232) was statistically significant. There was a statistically significant difference between the treatment groups in the percentage of subjects achieving a reduction to a physiologic glucocorticoid daily dose (≤ 11 mg/m²/day hydrocortisone equivalents adjusted for BSA) at Week 24, while androstenedione was controlled ($\leq 120\%$ of baseline or $\leq$ ULN for age and sex): 62.7% for the crinecerfont group and 17.5% for the placebo group (see [Figure 10](#)).

The three key secondary endpoints—change from baseline in HOMA-IR, percent change from baseline in weight, and change from baseline in total fat mass—were not statistically significant.

Table 17. Primary Analysis of Key Secondary Endpoints

Secondary Endpoint	Placebo	Crinecerfont 100 mg
Serum androstenedione (ng/dL) at Week 4		
N	60	122
Baseline, mean (SD)	590 (74)	634 (72)
LSM change from baseline	46 (51)	-299 (38)
Difference in LSM (95% CI) ^a		-344 (-457, -232)
p-value		<0.0001
Reduction to physiologic glucocorticoid dose while maintaining androstenedione control at Week 24		
N	60	122
Number of subjects, n	57	118
Responders, n (%)	10 (17.5)	74 (62.7)
p-value ^b		<0.0001

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Secondary Endpoint	Placebo	Crinecerfont 100 mg
Serum androstenedione (ng/dL) at Week 4		
HOMA-IR at Week 24		
N	59	122
LSM change from baseline (SE)	-0.36 (0.28)	-0.65 (0.21)
Difference in LSM (95% CI) ^a		-0.29 (-0.89, 0.32)
p-value		0.35
Percent weight at Week 24 (kg)		
N	60	122
LSM change from baseline (SE)	-0.1 (0.72)	-1.5 (0.53)
Difference in LSM (95% CI) ^a		-1.4 (-3.0, 0.2)
p-value		0.086
Percent total fat mass at Week 24		
N	60	122
LSM change from baseline	-1.0 (0.98)	-0.1 (0.66)
Difference in LSM (95% CI) ^a		-0.9 (-1.0, 2.9)
p-value		0.35

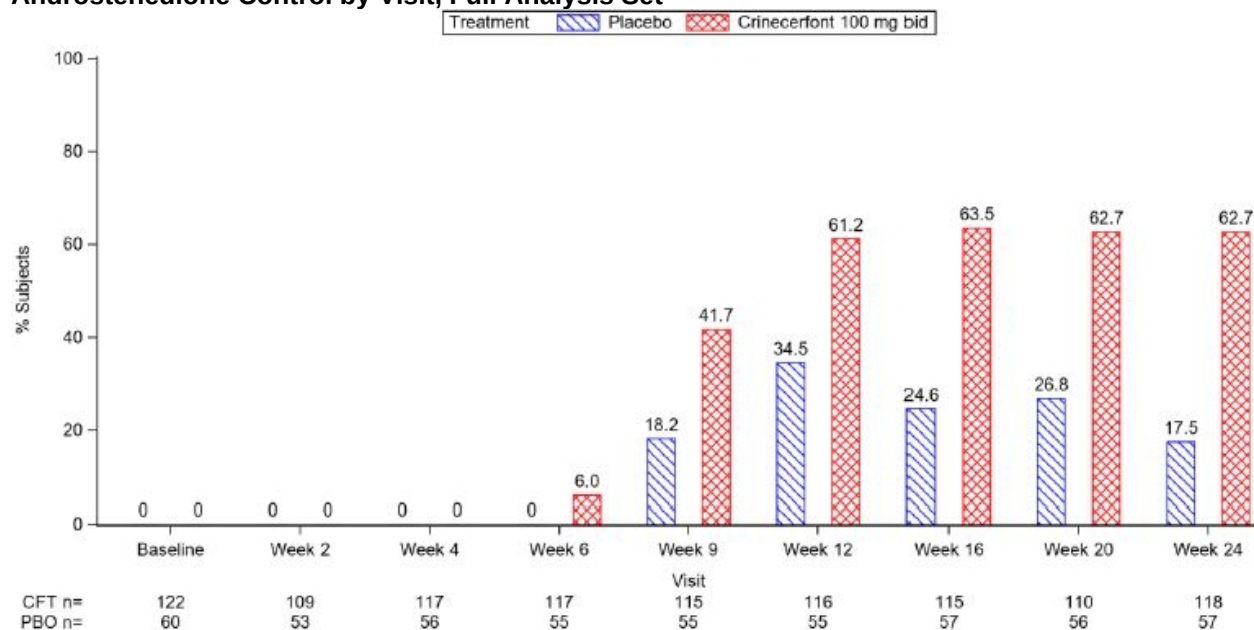
Source: Source Data: ADGCM, ADPDM, ADMETAB, ADWEIGHTMI, ADSL and statistical reviewer's analysis

^a Difference in crinecerfont minus placebo.

^b P-value is from CMH test comparing treatment groups adjusting for stratification factors (sex, glucocorticoid type, and total daily glucocorticoid regimen).

Abbreviations: CI, confidence interval; CMH, Cochran-Mantel-Haenszel; HOMA-IR, homeostatic model assessment of insulin resistance; LSM, least-squares mean; SD, standard deviation; SE, standard error

Figure 10. Achievement of a Reduction to Physiologic Glucocorticoid Doses While Maintaining Androstenedione Control by Visit, Full Analysis Set



Source: ADGC, ADSL and statistical reviewer's analysis

Percentages were based on the number of subjects in the full analysis set with observed data at each visit.

Abbreviations: bid, twice daily; CFT, crinecerfont 100 mg bid; PBO, placebo

To align with clinical guidelines ([Speiser et al. 2018](#)), an exploratory analysis was performed of subjects with androstenedione levels of $\leq$ ULN for age and sex at Week 24 (excluding those with a Week 24 androstenedione level $>$ ULN) while on physiologic glucocorticoid doses. These results are supportive of the primary findings ([Table 18](#)). Given the mean baseline glucocorticoid daily dose of 16 mg/m²/day hydrocortisone equivalents in the crinecerfont group for this subgroup analysis, a decrease of 12% (placebo-subtracted difference) corresponds to a mean dose of 14 mg/m²/day, for an absolute mean decrease of 2 mg/m²/day hydrocortisone equivalents.

Table 18. Results of Exploratory Efficacy Endpoint Analysis for Subjects With Androstenedione Levels $\leq$ Upper Limit of Normal at Week 24, Trial NBI-74788-CAH3003

Efficacy Endpoint	Crinecerfont (n=59)	Placebo (n=17)	Placebo-Subtracted Difference
LSM (SEM) percent change from baseline in glucocorticoid daily dose* at Week 24, while Week 24 androstenedione levels are controlled ($\leq$ ULN for age and sex)	-35.7% (3.1)	-23.8% (4.3)	-12% (95% CI: -20, -3.7) nominal p=0.005
Proportion with reduction in glucocorticoid daily dose to $\leq$ 11 mg/m ² /day hydrocortisone equivalent at Week 24 while androstenedione levels are controlled ($\leq$ ULN for age and sex)	51/59 (86.4%)	9/17 (52.9%)	33.5% nominal p=0.026

Source: clinical reviewer-generated from Applicant's submitted analysis

*Daily glucocorticoid dose is in hydrocortisone equivalents

Abbreviations: CI, confidence interval; LSM, least-squares mean; SEM, standard error of the mean; ULN, upper limit of normal

Also supportive of the primary findings is an analysis of available data from the open-label treatment period which showed sustainment of the findings. As shown in [Table 19](#) and in [Figure 11](#), the percentage reduction in daily glucocorticoid dose was consistent between Week 24 and Month 12 for subjects receiving crinecerfont for the entire 12-month period. The proportion of subjects who were able to reduce their total glucocorticoid dose to $\leq$ 11 mg/m²/day by Month 12 (42.4%) decreased compared to Week 24 (62.7%) in subjects receiving crinecerfont for one year ([Table 19](#) and [Figure 10](#)). However, the data analysis at Month 12 included only 59 of the 122 subjects in the crinecerfont/crinecerfont group and 28 of the 60 subjects in the placebo/crinecerfont group treated during the open-label period by the data cutoff date.

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Table 19. Results of Exploratory Efficacy Endpoint Analysis for Subjects Treated With Crinecerfont During the 12-Month Study Period, Trial NBI-74788-CAH3003

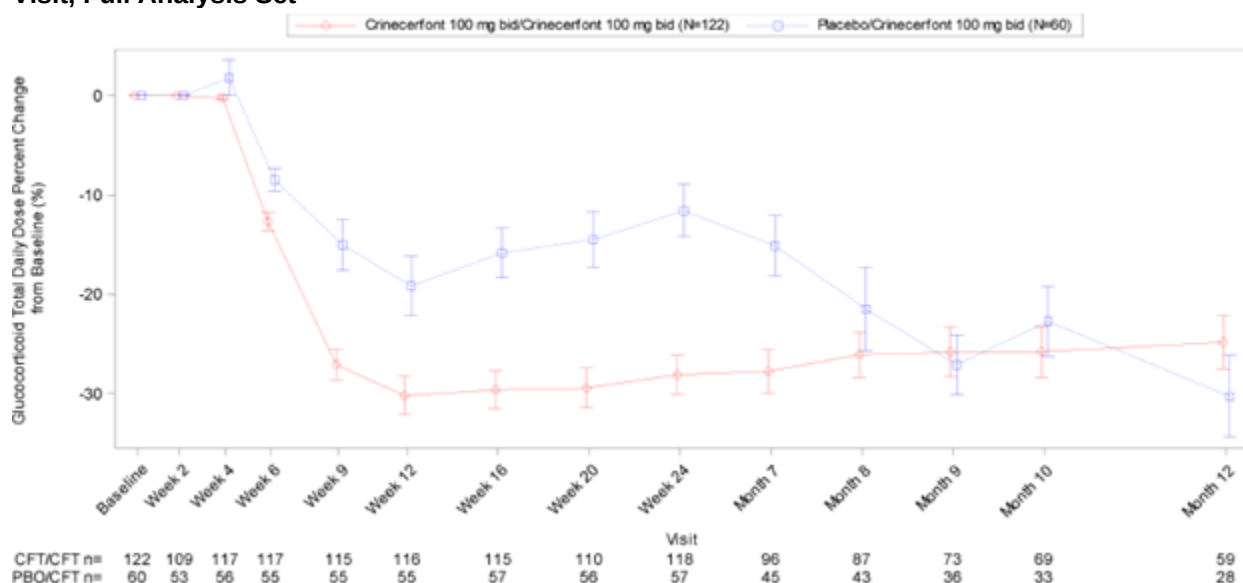
Efficacy Endpoint	Crinecerfont (Week 24) (n=122)	Placebo/ Crinecerfont (Month 12) (n=28)	Crinecerfont/ Crinecerfont (Month 12) (n=59)
Mean (SEM) percent change from baseline in glucocorticoid daily dose while androstenedione levels are controlled ($\leq 120\%$ of baseline or $\leq \text{ULN}$ for age and sex)	-27.3% (2.4) [least square mean (SEM)]	-30.3% (4.1)	-24.8% (2.7)
Proportion with reduction in glucocorticoid daily dose to $\leq 11 \text{ mg/m}^2/\text{day}$ hydrocortisone equivalent while androstenedione levels are controlled ($\leq 120\%$ of baseline or $\leq \text{ULN}$)	74/122 (62.7%)	16/28 (57.1%)	25/59 (42.4%)

Source: Clinical reviewer-generated from the statistical analysis and Applicant's submitted analysis

Daily glucocorticoid dose is in hydrocortisone equivalents

Abbreviations: SEM, standard error of the mean, ULN, upper limit of normal

Figure 11. Mean ($\pm$ SEM) Percent Change From Baseline in Glucocorticoid Total Daily Dose by Visit, Full Analysis Set



Source: Trial CAH3003 clinical study report, Figure 11, p. 86; data source: Figure 14.2.1.1.9

Glucocorticoid daily dose is presented in hydrocortisone equivalents adjusted for BSA [$\text{mg/m}^2/\text{day}$].

Subjects were randomized to crinecerfont 100 mg bid or placebo on Day 1. At Week 24, all subjects received open-label crinecerfont through Month 12. Treatment group labels indicate what the subject was randomized to on Day 1 and then followed by open-label crinecerfont 100 mg bid.

Baseline is defined as the last value before study treatment dosing on Day 1.

Values on the x axis have been shifted slightly for ease of reading.

Abbreviations: bid, twice daily; BSA, body surface area; CFT, crinecerfont 100 mg bid; PBO, placebo

12.2.3. Trial CAH2006

12.2.3.1. Design, Trial CAH2006

Overall Design

Trial CAH2006 is titled “A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of crinecerfont in pediatric subjects with classic congenital adrenal hyperplasia, followed by open-label treatment.” The study design is appropriate to demonstrate efficacy and is depicted in [Figure 12](#). This phase 3 trial consisted of a 4-week screening period, a 28-week double-blind placebo-controlled treatment period, and a 6-month open-label treatment period through Week 52. The primary objective of the study was to evaluate the efficacy of crinecerfont, compared with placebo, in reducing adrenal androgen levels during a glucocorticoid-stable period.

Randomized, Double-Blind, Placebo-Controlled Treatment Period (Day 1 to Week 28)

A total of 103 pediatric subjects aged 4 to 17 years with classic CAH caused by 21-hydroxylase deficiency and who required supraphysiologic doses of glucocorticoids to control androgen excess (>12 mg/m²/day hydrocortisone equivalents) were randomized in a 2:1 ratio (active:placebo) to receive a weight-based dosage of crinecerfont orally twice daily with breakfast and the evening meal (25 mg oral solution twice daily for subjects weighing 10 to less than 20 kg; 50 mg oral solution twice daily for subjects weighing 20 to less than 55 kg; and 100 mg oral capsule for subjects weighing 55 kg or more) or placebo. Randomization was stratified by pubertal stage (Tanner breast or genital stage 1 or 2 versus 3, 4, or 5) and sex.

During the first 4 weeks of the study, subjects maintained their baseline glucocorticoid regimen. Serum androstenedione and 17-hydroxyprogesterone levels were measured at Week 4 to evaluate the change from baseline.

From Week 4 to Week 28, glucocorticoid dosage was adjusted to a target of 8 to 10 mg/m²/day hydrocortisone equivalents while maintaining goal androstenedione levels ($<ULN$ for sex and age or if pubertal, pubertal stage; or $\leq 120\%$ of the subject's baseline) as long as there was no evidence of glucocorticoid insufficiency.

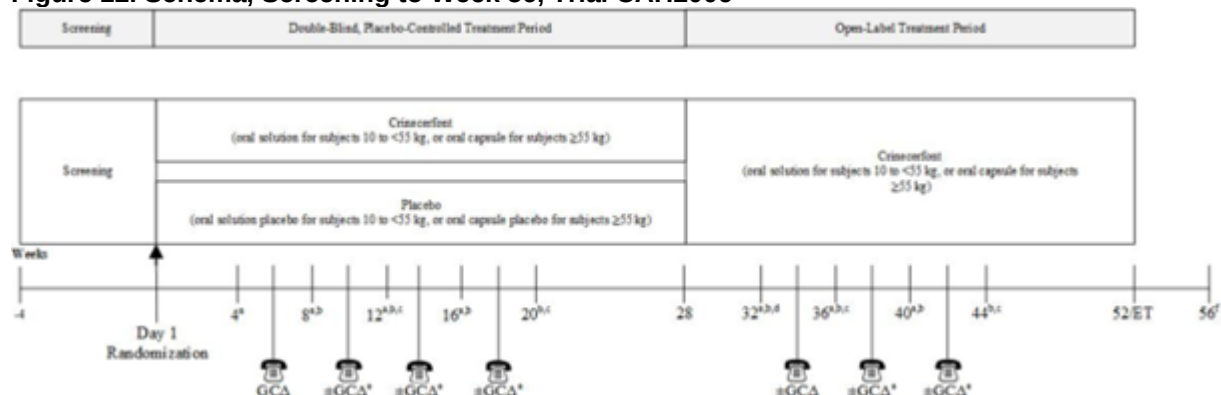
Open-Label Treatment Period (Week 28 to Week 52)

At Week 28, subjects transitioned to a 6-month open-label period during which all subjects received a crinecerfont dosage based on their Week 28 body weight. During Week 32 through Week 52, glucocorticoid dosage was reduced as tolerated if androstenedione levels were controlled ($\leq 120\%$ of baseline or $\leq ULN$ for sex, age, or pubertal stage) to a goal of 8 to 10 mg/m²/day hydrocortisone equivalents by Week 52.

In all parts of the study allowing for glucocorticoid dose reduction, the attempted dose reduction was approximately 1 to 4 mg/m²/day per month.

After Week 52, subjects could enter an open-label extension period allowing for crinecerfont dose adjustment with the goal of maintaining adequate disease control at the lowest possible glucocorticoid dosage.

Figure 12. Schema, Screening to Week 56, Trial CAH2006



Source: Clinical study report CAH2006, Figure 1, p. 25

^a If needed, the investigator contacted the subject/guardian once laboratory results were available in order to instruct the subject/guardian on any GC dose changes and arrange any needed follow-up.

^b At home or the study site. At Weeks 16 and 40, at home was an option if height was not required.

^c These visits occurred only if there was any preceding GC dose modification during the same treatment period.

^d Subjects had further GC dose adjustment starting at Week 32 only if their Week 32 GC dose was >11 mg/m²/day.

^e GC dose adjustments occurred in as few as one or up to three or four steps, depending on the starting and target GC doses and the amount of dose adjustment at each step.

^f Subjects who completed the Week 52 visit and did not enter the open-label extension underwent a safety follow-up visit approximately 4 weeks after the last dose of study drug.

Abbreviations: ET, early termination; GC, glucocorticoid

Efficacy Endpoints

The primary efficacy endpoint was change from baseline (CFB) in serum androstenedione at Week 4.

Key secondary efficacy endpoints were:

- Change from baseline in serum 17-OHP at Week 4
- Percent change from baseline in glucocorticoid daily dose (in hydrocortisone equivalents adjusted for BSA [mg/m²/day]) at Week 28), while Week 28 serum androstenedione was controlled ($\leq 120\%$ of the baseline value or $\leq \text{ULN}$, according to sex and either age [for Tanner stage 1] or pubertal stage [for Tanner stages 2 to 5])

12.2.3.2. Eligibility Criteria, Trial CAH2006

The eligibility criteria are reflective of the patient population with uncontrolled disease who would benefit from a reduction in glucocorticoid dose. Study subjects were required to be taking supraphysiologic glucocorticoid doses (i.e., total daily dosage >12 mg/m²/day in hydrocortisone dose equivalents). Androstenedione levels (prior to morning glucocorticoid dose) were required to be greater than the midpoint of the reference range and 17-hydroxyprogesterone levels (prior to the morning glucocorticoid dose) were required to be greater than twice the upper limit of normal. Key eligibility criteria are summarized below.

Inclusion Criteria

- Male and nonpregnant and nonlactating female subjects aged 2 to 17 years of age with minimum body weight of at least 15 kg and medically confirmed diagnosis of classic CAH due to 21-hydroxylase deficiency based on standard medically accepted criteria (i.e., elevated 17-OHP, confirmed CYP21A2 genotype, or diagnostic results after cosyntropin stimulation testing).
- Requiring a supraphysiologic glucocorticoid dose regimen (i.e., >12 mg/m²/day in hydrocortisone dose equivalents, that had been stable for at least 1 month prior to screening, is intended for chronic use, and consists only of one or more of the following orally administered glucocorticoids: hydrocortisone, prednisone, prednisolone, or methylprednisolone;)
- Receiving a morning dose of glucocorticoid
- Androstenedione level (prior to morning glucocorticoid dose) greater than the midpoint of the reference range, according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5)
- 17-hydroxyprogesterone level (prior to the morning glucocorticoid dose) $>2\times$ ULN according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5)
- If treated with fludrocortisone, dose should be stable for at least 1 month prior to screening
- Upright PRA (in the absence of medications that confound interpretation of PRA) during screening $<3\times$ ULN and $>$ lower limit of normal on the subject's usual sodium intake. If PRA $>2\times$ ULN and $<3\times$ ULN, the subject must have normal age-specific systolic blood pressure and heart rate and serum potassium $<$ ULN

Exclusion Criteria

- Forms of CAH other than 21-hydroxylase deficiency
- History of other endocrinologic conditions requiring chronic daily therapy with oral glucocorticoids
- Determined to be an increased risk of adrenal crisis
- Presence of a clinically significant medical condition or chronic disease (including history of neurological, hepatic, renal, cardiovascular, gastrointestinal, significant malabsorption, hematologic, pulmonary, psychiatric, or endocrine disease [excluding CAH]) that in the investigator's opinion would preclude the subject's participation in the study or confound interpretation of study outcome
- History of malignancy, unless successfully treated and considered to be cured
- History of clinically concerning cardiac arrhythmia (including long QT syndrome) or prolongation of screening (pretreatment) QT interval corrected for heart rate using Fridericia's correction (QTcF) of >450 msec (males) or >470 msec (females)

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- Evidence of chronic renal or liver disease based on any of these screening laboratory test abnormalities:
 - Estimated glomerular filtration rate <60 mL/min/1.73 m²
 - Aspartate aminotransferase $>2\times$ ULN
 - Alanine aminotransferase $>2\times$ ULN
 - Total bilirubin $>1.5\times$ ULN unless due to a documented diagnosis of Gilbert's syndrome
- Any of the following hematologic abnormalities at screening:
 - Hemoglobin <10 g/dL (age <6 years) or <11 g/dL (age ≥ 6 years)
 - White blood cell count $<4.0\times 10^3/\text{mm}^3$
 - Platelet count $<100,000/\text{mm}^3$
 - Absolute neutrophil count $<1.0\times 10^3/\text{mm}^3$
- Any of the following coagulation abnormalities at screening:
 - Activated partial thromboplastin time that exceeds ULN by more than 5 seconds
 - Prothrombin time expressed as international normalized ratio (INR) >1.4 , unless the subject is on anticoagulant treatment that affects INR
- Screening serum sodium <130 mmol/L
- History or presence of substance dependence or substance or alcohol abuse
- At significant risk of suicidal or violent behavior; for subjects ≥ 6 years of age: presence of any suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) in the past 6 months before screening, or lifetime history of suicidal behavior based on the Columbia-Suicide Risk Scale were excluded

Contraception was required in female subjects of childbearing potential (i.e., past menarche and not surgically sterile) with fertile male partners from screening until the final study visit or 30 days after the last dose of study drug, whichever was longer.

The following medications were prohibited from 30 days before screening until the final study visit (or early termination):

- Any active investigational drug (not to be used within 30 days or five half-lives, whichever was longer)
- Orally administered glucocorticoids for indications other than CAH
- Strong inducers of CYP3A4 or CYP2B6 except topically administered medications
- Medications that affect cortisol or glucocorticoid metabolism (e.g., phenytoin, mitotane, phenobarbital, strong CYP3A4 inhibitors) except topically administered medications
- Exogenous testosterone treatment

12.2.3.3. Statistical Analysis Plan, Trial CAH2006

The full analysis set, defined as all randomized subjects regardless of adherence to study treatment administration, was used for all efficacy analyses. Continuous efficacy endpoints were analyzed using an analysis of covariance (ANCOVA) model assuming equal variance between the placebo and treatment groups. The ANCOVA model included the respective baseline measurement as a covariate and stratification factors and treatment group (crinecerfont; placebo) as factors. Categorical efficacy endpoints were analyzed using the Cochran-Mantel-Haenszel (CMH) test. The CMH test compared treatment groups (crinecerfont versus placebo) and included the stratification factors used in the randomization.

For analysis of the primary and key secondary endpoints, the fixed-sequence testing procedure described below was followed to control for the treatment-group comparisons of multiple endpoints. Each step in the sequential testing procedure used a two-sided 0.05 level of significance for the null hypothesis being tested; testing of hypotheses at each step of the procedure commenced only if all null hypotheses in prior steps were rejected.

1. Primary endpoint: change from baseline in serum androstenedione at Week 4.
2. Key secondary endpoint: change from baseline in serum 17-OHP at Week 4.
3. Key secondary endpoint: percent change from baseline in daily glucocorticoid dose (in hydrocortisone dose equivalents adjusted for BSA) at Week 28, while Week 28 serum androstenedione was $\leq 120\%$ of the baseline value or $\leq \text{ULN}$, according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5).

Missing data imputation for the primary and key secondary endpoints was handled similar to Trial CAH3003, i.e., for the primary and key secondary endpoints, the following steps were taken:

- For subjects on study drug who were missing the endpoint at the timepoint of interest, their missing Week 4 (or Week 28 for secondary endpoints) data were imputed from Completers (subjects who completed through the time of the endpoint on study drug) within the same treatment group.
- For subjects in the crinecerfont treatment group off study drug prior to the timepoint of interest who were missing the endpoint at the timepoint of interest, their missing endpoint was imputed from subjects who were classified as “retrieved dropouts” (subjects in the FAS who discontinued study drug but remained in the study and had an evaluable measurement). If there were five or fewer retrieved dropouts, the missing endpoint values would be imputed from subjects in the placebo treatment group. For subjects in the placebo treatment group, missing data were imputed using nonmissing data from subjects in the placebo treatment group.

12.2.3.4. Results of Analyses, Trial CAH2006

12.2.3.4.1. Disposition, Baseline Demographics and Baseline Clinical Characteristics

Disposition During Double-Blind Treatment Period (Baseline to Week 28)

A total of 103 subjects were randomized (69 crinecerfont; 34 placebo, [Table 20](#)). All subjects were included in the full analysis set. Most subjects (95.7% crinecerfont; 91.2% placebo) completed the study treatment. Reasons for study discontinuation (and study treatment discontinuation) before Week 28 were withdrawal by subject (1.4% crinecerfont; 8.8% placebo) and AE (2.9% crinecerfont; 0% placebo; see Section [13.6.3.4](#)). The 3 subjects in the crinecerfont group who were reported to have discontinued study treatment (and the study) by Week 28 discontinued the study after completing the Week 28 visit and thus had study data contributing to the key secondary endpoint of glucocorticoid dose.

Table 20. Subject Disposition, All Randomized Subjects

Disposition Category	Placebo (N=34) n (%)	Crinecerfont (N=69) n (%)	All Subjects (N=103) n (%)
Received study drug	33 (97.1)	69 (100)	102 (99.0)
Completed study treatment through Week 28	31 (91.2)	66 (95.7)	97 (94.2)
Completed study through Week 28	31 (91.2)	66 (95.7)	97 (94.2)
Discontinued study treatment prior to Week 28	3 (8.8)	3 (4.3)	6 (5.8)
Withdrawal by subject	3 (8.8)	1 (1.4)	4 (3.9)
Adverse event	0	2 (2.9)	2 (1.9)
Discontinued study prior to Week 28	3 (8.8)	3 (4.3)	6 (5.8)
Withdrawal by subject	3 (8.8)	1 (1.4)	4 (3.9)
Adverse event	0	2 (2.9)	2 (1.9)

Source: ADSL dataset for Trial CAH2006, statistical reviewer's analysis
Percentages are based on the number of subjects randomized (N).

Disposition During Open-Label Treatment Period (Weeks 28 to 52)

Of the 103 randomized subjects, 97 (97%) completed the double-blind treatment period. All 97 subjects entered the open-label treatment period (66 crinecerfont; 31 placebo) and were treated with open-label crinecerfont, with dosing recalculated based on the current body weight at Week 28. As of the data cutoff date (August 9, 2023), 45% (48% placebo/crinecerfont; 44% crinecerfont/crinecerfont) completed the study through Week 52 and are included in the efficacy analysis. Data from subjects who had not yet completed the open-label treatment period through Week 52 as of the data cutoff date are not included in the efficacy analyses but are included in the safety analysis. The remainder of subjects who entered the open-label treatment period completed treatment after the data cutoff date.

Disposition During Open-Label Extension (Week 52 Onward)

All 97 subjects who started the open-label treatment period completed open-label treatment through Week 52. Of the 97 who completed the open-label treatment period, 93 (97%) continued in the open-label extension.

Baseline Demographics and Clinical Characteristics

Subjects 2 years to 17 years of age were eligible for the study. Randomization in the study was stratified by pubertal stage (Tanner breast or genital stage 1 or 2 versus 3, 4, or 5) and sex. Demographics were generally similar between the treatment groups ([Table 21](#)). The mean age of randomized subjects was 12.1 years (range 4.6 to 17.8 years). Approximately 45% of randomized subjects in each treatment group were <12 years of age. There was an equal distribution of male and female subjects in both treatment groups. Most subjects in the study were White (63.1%) and not Hispanic or Latino (74.8%). Geographic region was the United States for 56.3% of subjects and outside the United States for 43.7% of subjects.

Baseline disease characteristics were generally similar between the treatment group and the placebo group ([Table 22](#)). Subjects, on average, were taking supraphysiologic glucocorticoid dosages and had mean androstenedione and 17-hydroxyprogesterone levels significantly above the clinical guideline-specified goal ranges (i.e., androstenedione within the reference range for age and sex ([Speiser et al. 2018](#))). A target 17-hydroxyprogesterone level of less than approximately 1200 ng/dL for children with CAH has been suggested ([Merke 2008](#)).

The mean glucocorticoid total daily dose in hydrocortisone equivalents was 16.4 mg/m²/day. In pediatrics, glucocorticoid dosages of 8 to 10 mg/m²/day hydrocortisone equivalent are clinically accepted as physiologic replacement ([Husebye et al. 2021](#)).

The mean androstenedione level was 431 ng/dL prior to the morning glucocorticoid dose (about 3 to 4 times the goal of less than the upper normal range). The androstenedione reference range for prepubertal males and females is up to about 50 ng/dL. During puberty, the androstenedione reference range varies by pubertal stage but generally ranges from a lower limit of 30 to 65 ng/dL to an upper limit of 65 to 210 ng/dL for males and a lower limit of 40 to 80 ng/dL to an upper limit of 100 to 240 ng/dL for females.

The mean 17-hydroxyprogesterone level was 8682 ng/dL (about 7 times the suggested goal of less than approximately 1200 ng/dL) prior to the morning glucocorticoid dose. The 17-OHP reference range for prepubertal males and females is about 0 to 90 ng/dL. During puberty, the 17-hydroxyprogesterone reference range varies by pubertal stage but generally ranges from a lower limit of 0 to 30 ng/dL to an upper limit of 115 to 180 ng/dL for males and a lower limit of 10 to 20 ng/dL to an upper limit of 100 to 265 ng/dL for females.

There were no enrolled pediatric subjects with body weight <20 kg. Therefore, the 25 mg bid solution was not tested in this trial (see [Section 12.3](#) for further details). There were 51 subjects in the 20 to <55 kg weight band (37 crinecerfont, 14 placebo) and 52 subjects in the ≥55 kg weight band (32 crinecerfont, 20 placebo).

Table 21. Subject Demographics, Full Analysis Set, Trial NBI-74788-CAH2006

Characteristic	Placebo (N=34)	Crinecerfont (N=69)	All Subjects (N=103)
Age (years)			
n	34	69	103
Mean	12.1	12.0	12.1
SD	3.69	3.41	3.48
Median	12.2	12.6	12.6
Min, max	4.6, 17.8	5.3, 17.8	4.6, 17.8

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

Characteristic	Placebo (N=34)	Crinecerfont (N=69)	All Subjects (N=103)
Age categories			
2 to <12 years	16 (47.1)	31 (44.9)	47 (45.6)
12 to 17 years	18 (52.9)	38 (55.1)	56 (54.4)
Sex			
Male	18 (52.9)	35 (50.7)	53 (51.5)
Female	16 (47.1)	34 (49.3)	50 (48.5)
Ethnicity			
Hispanic or Latino	3 (8.8)	8 (11.6)	11 (10.7)
Not Hispanic or Latino	25 (73.5)	52 (75.4)	77 (74.8)
Not collected	6 (17.6)	9 (13.0)	15 (14.6)
Race			
American Indian or Alaska Native	0	1 (1.4)	1 (1.0)
Asian	2 (5.9)	7 (10.1)	9 (8.7)
Black or African American	0	3 (4.3)	3 (2.9)
White	23 (67.6)	42 (60.9)	65 (63.1)
Native Hawaiian or Other Pacific Islander	0	1 (1.4)	1 (1.0)
Other	2 (5.9)	3 (4.3)	5 (4.9)
Multiple	1 (2.9)	3 (4.3)	4 (3.9)
Not collected	6 (17.6)	9 (13.0)	15 (14.6)
Region			
United States	14 (41.2)	44 (63.8)	58 (56.3)
Outside United States	20 (58.8)	25 (36.2)	45 (43.7)
BMI standard deviation score			
Mean	1.12	1.20	1.18
SD	1.04	0.88	0.93
Median	1.30	1.25	1.26
Min, max	-1.0, 2.8	-0.9, 2.8	-1.0, 2.8
Tanner stage (breast or testicular), n (%)			
Stage 1	12 (35.3)	18 (26.1)	30 (29.1)
Stage 2	2 (5.9)	10 (14.5)	12 (11.7)
Stage 3	5 (14.7)	8 (11.6)	13 (12.6)
Stage 4	4 (11.8)	15 (21.7)	19 (18.4)
Stage 5	11 (32.4)	18 (26.1)	29 (28.2)

Source: ADSL data and statistical reviewer's analysis

Percentages are based on the number of subjects in the full analysis set (N).

Abbreviations: BMI, body mass index; max, maximum; min, minimum; SD, standard deviation

Table 22. Baseline Disease Characteristics, Full Analysis Set, Trial NBI-74788-CAH2006

Characteristic	Placebo (N=34)	Crinecerfont (N=69)	All Subjects (N=103)
Serum androstenedione (ng/dL)–Day 1 pre-glucocorticoid dose values			
Mean	483.3	405.0	430.8
SD	455.6	464.1	460.6
Median	320.0	307.5	307.5
Min, max	8.5, 1765.0	6.0, 2851.5	6.0, 2851.5
Serum 17-OHP (ng/dL)–Day 1 pre- glucocorticoid dose values			
Mean	9026	8513	8682
SD	5563	7431	6847
Median	8205	5907	6440
Min, max	276, 22909	61, 27547	61, 27547

Characteristic	Placebo (N=34)	Crinecerfont (N=69)	All Subjects (N=103)
Daily glucocorticoid dose adjusted for BSA (mg/m ² /day) ^a			
Mean	16.3	16.5	16.4
SD	3.40	4.19	3.93
Median	15.5	15.9	15.6
Min, max	11.4, 24.9	12.1, 34.6	11.4, 34.6
Glucocorticoid type, n (%)			
Hydrocortisone alone	32 (94.1)	63 (91.3)	95 (92.2)
Prednisone, prednisolone, methylprednisolone, with or without hydrocortisone	2 (5.9)	6 (8.7)	8 (7.8)

Source: ADSL data and statistical reviewer's analysis

Baseline was defined as the last value prior to study drug dosing on Day 1.

^a Daily glucocorticoid dose is expressed in hydrocortisone equivalents.

Abbreviations: 17-OHP, 17-hydroxyprogesterone; BSA, body surface area; SD, standard deviation; min, minimum; max, maximum

12.2.3.4.2. Efficacy Results

Efficacy results for Trial CAH2006 include analysis of the completed double-blind period (i.e., Day 1 to Week 28) and an interim analysis of the available data for the ongoing open-label period (i.e., Week 28 to Week 52) at the data cutoff (August 9, 2023).

12.2.3.4.2.1. Primary Analysis

For the primary efficacy endpoint, the LS mean change from baseline in serum androstenedione at Week 4 following the initial 4-week glucocorticoid stable dose period, was -196.8 (standard error [SE] 39.4) ng/dL for the crinecerfont group compared with 71.0 (SE 56.2) ng/dL for the placebo group. The LS mean treatment difference (crinecerfont - placebo) of -267.8 ng/dL (95% CI: -403.4, -132.1) was statistically significant (p-value=0.0002) ([Table 23](#)).

Table 23. ANCOVA Analysis of Change From Baseline in Serum Androstenedione (ng/dL) at Week 4, Full Analysis Set, Trial NBI-74788-CAH2006

Parameter	Placebo	Crinecerfont
N	34	69
Baseline, mean (SD)	483 (455.6)	405.0 (464.1)
LSM change from baseline (SE)	-71.0 (56.2)	-196.8 (39.4)
Difference in LSM		-267.8
(95% CI) ^a		(-403.4, -132.1)
p-value		0.0002

Source: ADGCM, ADSL data and statistical reviewer's analysis

^a Difference is Crinecerfont minus placebo.

Least-squares (LS) mean based on the ANCOVA model which includes baseline GC dose as a covariate, and treatment group and stratification factors as fixed effects. Summary statistics are based on observed data and ANCOVA analysis results are based on multiply imputed data.

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval; LSM, least-squares mean; SD, standard deviation; SE, standard error

For the primary endpoint, most of the randomized subjects were receiving study drug and had observed data for this endpoint at Week 4 (98.6% crinecerfont; 97.1% placebo) ([Table 24](#)). Overall missing data for the primary endpoint was minimal (2%).

Table 24. Summary of Missing Primary Endpoint at Week 4, Full Analysis Set, Trial NBI-74788-CAH2006

Subject Type	Placebo (N=34) n(%)	Crinecerfont (N=69) n (%)	All Subjects (N=103) n (%)
Completers	33 (97.1)	68 (98.6)	101 (98.1)
Retrieved dropouts	0	0	0
Nonretrieved dropouts	1 (2.9)	1 (1.4)	1 (1.0)
On-drug missing endpoint	0	1 (1.4)	1 (1.0)

Source: Statistical reviewer's analysis

A two-way tipping point sensitivity analysis was performed to assess the robustness of the primary efficacy analysis. Significance at $p < 0.05$ was maintained for change from baseline in serum androstenedione at Week 4 when the delta shift for the multiply imputed values was up to 2006 ng/dL for crinecerfont or -2006 ng/dL for placebo. [Table 25](#) contains all combinations of delta values that tip the result from statistically significant to not statistically significant. The tipping point ($p \geq 0.05$) was reached when the combined delta shift was 3926 ng/dL or greater (1920 ng/dL for crinecerfont and -2006 ng/dL for placebo), which is an extreme value that supports the robustness of the primary results.

Table 25. P-Value for Two-Way Tipping Point Sensitivity Analysis of Primary Endpoint, Full Analysis Set

Delta Adjustment for Placebo	Delta Adjustment for Crinecerfont					
	0	1891	1920	1948	1977	2006
0	0.0002	0.0042	0.0044	0.0046	0.0049	0.0051
-1891	0.0072	0.0432	0.0444	0.0456	0.0469	0.0482
-1920	0.0077	0.0448	0.0460	0.0473	0.0486	0.0499
-1948	0.0082	0.0464	0.0477	0.0489	0.0502	0.0516
-1977	0.0087	0.0481	0.0494	0.0507	0.0520	0.0534
-2006	0.0092	0.0498	0.0512	0.0525	0.0538	0.0553

Source: ADGC, ADGCM data and Statistical Reviewer's analysis

Results of the primary analyses of the two key secondary endpoints are shown in [Table 26](#). The LS mean change from baseline in serum 17-OHP at Week 4 was -5865 (SE 572.0) ng/dL for the crinecerfont group compared with 556 (SE 818) ng/dL for the placebo group. The LS mean treatment difference (crinecerfont - placebo) of -6421 ng/dL (95% CI: -8387, -4454) was statistically significant. Similarly, the percent change from baseline in glucocorticoid daily dose at Week 28, while Week 28 androstenedione was controlled at $\leq 120\%$ of baseline or $\leq \text{ULN}$ for sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5), was statistically significant. The LS mean reduction in glucocorticoid daily dose was -18.0% (SE 1.8) for the crinecerfont group and 5.6% (2.7) for the placebo group, with an LS mean difference (crinecerfont - placebo) of -23.5% (95% CI: -29.9, -17.2).

Table 26. Primary Analysis of Key Secondary Endpoints

Secondary Endpoint	Placebo	Crinecerfont
Serum 17-OHP (ng/dL) at Week 4		
N	34	69
Baseline, mean (SD)	9026 (5563)	8513 (7431)
LSM change from baseline (SE)	556 (818)	-5865 (572)
Difference in LSM		-6421
(95% CI) ^a		(-8387, -4454)
p-value ^b		<0.0001
Glucocorticoid daily dose while maintaining androstenedione at Week 28		
N	34	69
Baseline, mean (SD)	16.3 (3.4)	16.5 (4.19)
LSM percent change from baseline (SE)	5.6 (2.65)	-18.0 (1.82)
Difference in LSM percentage		-23.5
(95% CI) ^a		(-29.9, -17.2)
p-value		<0.0001

Source: Source Data: ADGCMI, ADPDMI, ADMETAB, ADWEIGHTMI, ADSL and statistical reviewer's analysis

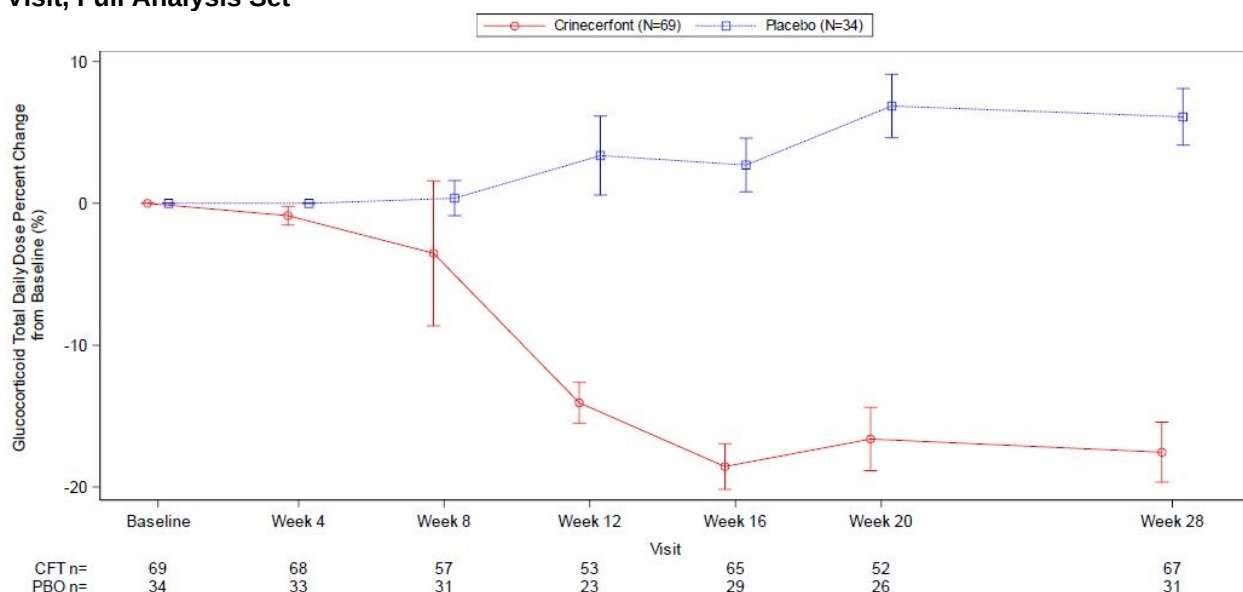
^a Difference is Crinecerfont minus placebo.

Least-squares (LS) mean based on the ANCOVA model which includes baseline GC dose as a covariate, and treatment group and stratification factors as fixed effects. Summary statistics are based on observed data and ANCOVA analysis results are based on multiply imputed data.

Abbreviations: SD, standard deviation; SE, standard error; LSM, least-squares mean; ANCOVA, analysis of covariance; CI, confidence interval; GC, glucocorticoid; 17-OHP, 17-hydroxyprogesterone

[Figure 13](#) shows the mean (SE) percent change from baseline in glucocorticoid dose with androstenedione control by visit during the double-blind period. Consistent with the protocol, there was minimal change in glucocorticoid dose at Week 4. Starting at Week 4, there was a progressive decrease in glucocorticoid dose until Week 16 that was maintained to Week 28 in the crinecerfont group, whereas the glucocorticoid dose in the placebo group increased and remained above baseline through Week 28.

Figure 13. Mean ($\pm$ SEM) Percent Change From Baseline of Glucocorticoid Total Daily Dose by Visit, Full Analysis Set



Source: ADGC, ADSL data and statistical reviewer's analysis

Subjects not meeting the androstenedione control criteria will have their glucocorticoid daily dose percent change from baseline value set to zero at each visit where control is not met.

Abbreviations: CFT, crinecerfont 100 mg bid; PBO, placebo

In the primary analysis, if a subject did not meet androstenedione control criteria, the change (and percentage change) in glucocorticoid daily dose from baseline was set to zero at each visit where control was not met. As an exploratory analysis, the primary analysis of this key secondary endpoint was repeated without setting the glucocorticoid daily dose to zero for these subjects. In this analysis, the least square mean difference (-25.9% and 95% CI: [-32.5, -19.2]) at Week 28 was similar to that of the primary analysis.

Given the mean baseline glucocorticoid daily dose of 16.5 mg/m²/day hydrocortisone equivalents in the crinecerfont group, a decrease of 18% (decrease observed in the crinecerfont group) would correspond to a dose of 13.5 mg/m²/day, for an absolute decrease of 3 mg/m²/day hydrocortisone equivalents. A decrease of 3 mg/m²/day hydrocortisone equivalents in pediatric subjects with CAH treated with supraphysiologic glucocorticoid dosages is clinically meaningful. See Section [12.2.2.4](#) for a discussion of the clinical meaningfulness of this reduction.

A secondary endpoint of clinical importance, reduction in physiologic glucocorticoid doses while maintaining androstenedione control (defined as serum androstenedione <120% of baseline or $\leq$ ULN, according to sex and either age for Tanner stage 1 or pubertal stage for Tanner stages 2 to 5) at Week 28, showed a 30% responder rate with crinecerfont versus a 0% responder rate for placebo ([Table 27](#)).

Table 27. Reduction to Physiologic Glucocorticoid Dose While Maintaining Androstenedione Control at Week 28, Full Analysis Set

Parameter	Placebo (N=34)	Crinecerfont (N=69)
Number of subjects, n	31	67
Responders, n (%)	0	20 (29.9)
Nominal p-value		0.0009

Source: ADGC, ADGCM, ADSL data and Statistical Reviewer's analysis.

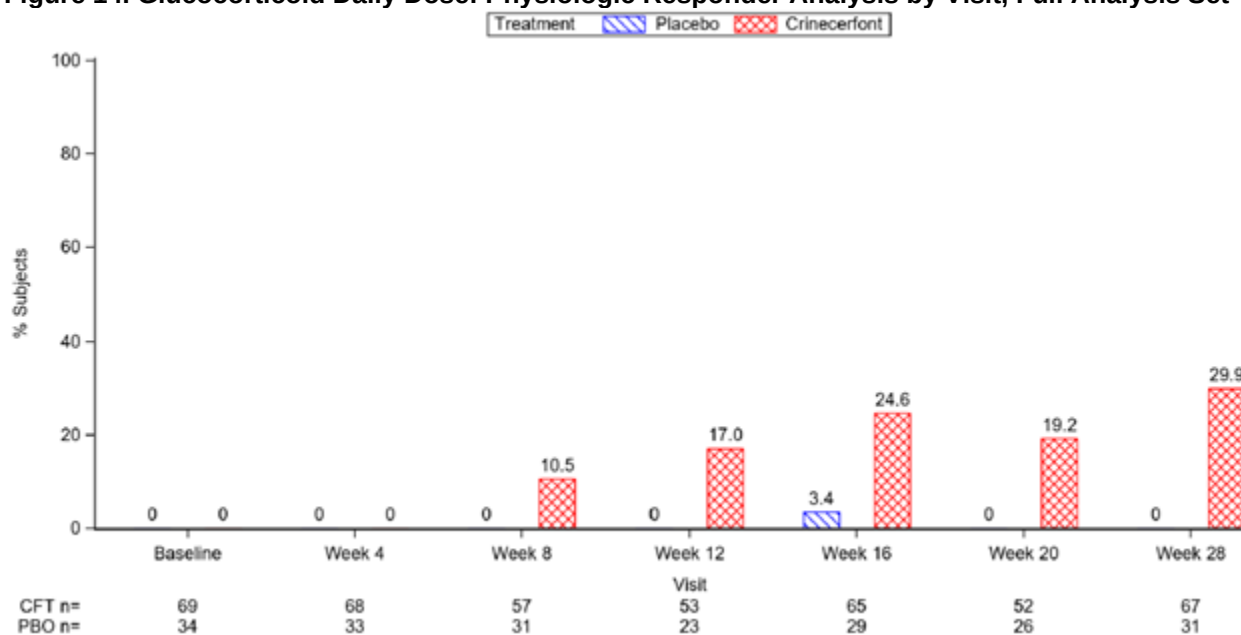
- A responder is defined as a subject who has achieved a reduction in glucocorticoid daily dose to physiologic levels (≤ 11 mg/m²/day in hydrocortisone dose equivalent adjusted for BSA) at Week 28, while Week 28 serum androstenedione is $\leq 120\%$ of the baseline value or $\leq$ ULN for sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5).

- P-value is from CMH test comparing treatment groups adjusting for stratification factors used in the randomization.

Abbreviations: ULN, upper limit of normal; CMH, Cochran-Mantel-Haenszel; BSA, body surface area

Figure 14 shows the percentage of subjects achieving a physiologic glucocorticoid dose with androstenedione control [$<120\%$ of baseline or $\leq$ ULN, according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5)] by visit during the double-blind period. The percentage of subjects in the crinecerfont group achieving this glucocorticoid dose with androstenedione control ranged from 10.5% to 29.9% starting at Week 8. In contrast, except for one subject (3.4%) in the placebo group who was a transient responder at the Week 16 visit, no subjects in the placebo group were able to achieve a physiologic glucocorticoid dose while maintaining androstenedione control during the 28-week double-blind period.

Figure 14. Glucocorticoid Daily Dose: Physiologic Responder Analysis by Visit, Full Analysis Set



Source: ADGC, ADSL and statistical reviewer's analysis

A responder was defined as a subject who achieved a reduction in glucocorticoid daily dose to physiologic levels (≤ 11 mg/m²/day in hydrocortisone equivalent adjusted for BSA) at the visit of interest, while androstenedione was controlled at $\leq 120\%$ of baseline or $\leq$ ULN for age and sex at that visit.

Percentages were based on the number of subjects in the full analysis set with observed data at each visit.

Abbreviations: BSA, body surface area; CFT, crinecerfont 100 mg bid; PBO, placebo; ULN, upper limit of normal

To align with clinical guidelines, an exploratory analysis was performed of subjects with androstenedione of $\leq$ ULN for sex and age or if pubertal, pubertal status, at Week 28 (excluding those with a Week 28 androstenedione level $>$ ULN) while on physiologic glucocorticoid doses. These results are supportive of the primary findings (Table 28). Given the mean baseline

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

glucocorticoid daily dose of 15 mg/m²/day hydrocortisone equivalents in the crinecerfont group, a decrease of 19.7% (decrease observed in the crinecerfont group) corresponds to a dose of 12 mg/m²/day, for an absolute decrease of 3 mg/m²/day hydrocortisone equivalents (the same absolute decrease as for the primary findings).

Table 28. Results of Exploratory Efficacy Endpoint Analysis for Subjects With Androstenedione Levels ≤Upper Limit of Normal at Week 28, Trial NBI-74788-CAH2006

Efficacy Endpoint	Crinecerfont (n=26)	Placebo (n=10)	Placebo-Subtracted Difference
LSM (SEM) percent change from baseline in glucocorticoid daily dose* at Week 28, while Week 28 androstenedione levels are controlled (≤ULN for sex and age or if pubertal, pubertal status)	-19.7% (2.7)	8.9% (4.5)	-28.5% (95% CI: -39.5, -17.6) Nominal p<0.0001
Proportion with reduction in glucocorticoid daily dose to ≤11 mg/m ² /day hydrocortisone equivalent at Week 24 while androstenedione levels are controlled (≤ULN for sex and age or if pubertal, pubertal status)	12/26 (46.2%)	0/10 (0%)	46.2% Nominal p=0.002

Source: clinical reviewer-generated from Applicant's submitted analysis

* Daily glucocorticoid dose is in hydrocortisone equivalents

Abbreviations: LSM, least-squares mean; SEM, standard error of the mean; ULN, upper limit of normal; CI, confidence interval

Also supportive of the primary findings is analysis of available data from the open-label treatment period which showed sustainment of the findings in subjects receiving crinecerfont for 52 weeks ([Table 29](#), [Figure 15](#), [Figure 10](#)). However, the data analysis at Week 52 included only 28 of the 69 subjects in the crinecerfont/crinecerfont group and 14 of the 34 subjects in the placebo/crinecerfont group treated during the open-label period by the data cutoff date.

Table 29. Results of Exploratory Efficacy Endpoint Analysis for Subjects Treated With Crinecerfont During the 52-Week Study Period, Trial NBI-74788-CAH2006

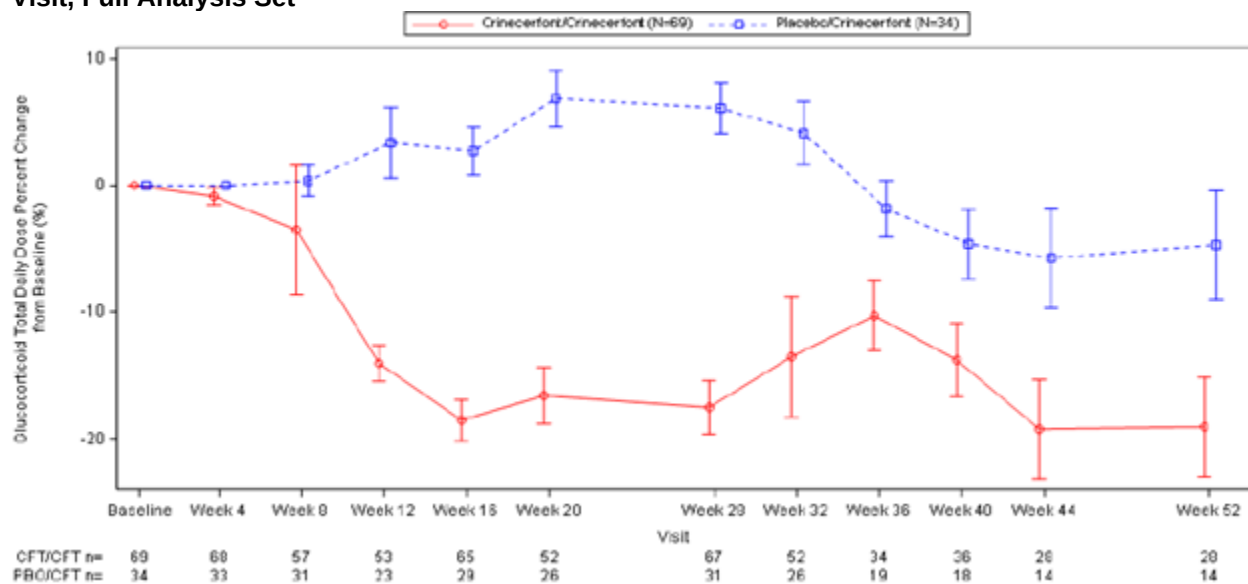
Efficacy Endpoint	Crinecerfont (Week 28) (n=69)	Placebo/ Crinecerfont (Week 52) (n=14)	Crinecerfont/ Crinecerfont (Week 52) (n=28)
Mean (SEM) percent change from baseline in glucocorticoid daily dose* at Week 28 or Week 52, while Week 28 or Week 52 androstenedione levels are controlled ($\leq$ ULN for sex and age or if pubertal, pubertal status)	-18% (1.8)	-4.7% (4.3)	-19.1% (3.9)
Proportion with reduction in glucocorticoid daily dose to ≤ 11 mg/m ² /day hydrocortisone equivalent at Week 28 or Week 52 while androstenedione levels are controlled ($\leq$ ULN for sex and age or if pubertal, pubertal status)	20/69 (29.9%)	2/14 (14.3%)	8/28 (28.6%)

Source: clinical reviewer-generated from Applicant's submitted analysis

* Daily glucocorticoid dose is in hydrocortisone equivalents

Abbreviations: SEM, standard error of the mean; ULN, upper limit of normal

Figure 15. Mean ($\pm$ SEM) Percent Change From Baseline of Glucocorticoid Total Daily Dose by Visit, Full Analysis Set



Source: Trial CAH2006, clinical study report, Figure 10, p. 90; data source: Figure 14.2.3.3.3

Baseline is defined as the last value prior to study drug dosing on Day 1.

Androstenedione control is defined as androstenedione $\leq 120\%$ of baseline or $\leq$ ULN, according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5). Subjects not meeting the androstenedione control criteria had their glucocorticoid daily dose change from baseline value set to zero at each visit if control was not met.

Subjects were randomized to crinecerfont or placebo on Day 1. At Week 28, all subjects received open-label crinecerfont through Week 52. Treatment group labels indicate what the subject was randomized to on Day 1 and the followed by open-label crinecerfont.

Values on the x axis have been shifted slightly for ease of reading.

Abbreviations: CFT, crinecerfont; PBO, placebo; ULN, upper limit of normal; SEM, standard error of the mean

12.3. Key Efficacy Review Issues

12.3.1. Appropriate Dosage in Pediatric Patients Weighing 10 kg to Less Than 20 kg

Issue

No pediatric subjects weighing 10 kg to less than 20 kg were enrolled in the pediatric phase 3 Trial CAH2006. Therefore, the proposed crinecerfont dosage of 25 mg twice daily (oral solution) for this patient population was not evaluated in a phase 3 clinical trial.

Background

The Applicant selected a dosing regimen of 25 mg bid for the pediatric 10 to <20 kg weight band based on exposure matching to the adult regimen of 100 mg twice daily using popPK modeling and simulation.

Assessment

Leveraging popPK modeling and simulation, an exposure-matching approach was employed by the Applicant to propose dosing regimens for pediatric patients by weight bands (10 to <20 kg, 20 to <55 kg, and ≥ 55 kg), corresponding to doses of 25 mg solution bid, 50 mg solution bid, and 100 mg capsule bid, respectively. The simulated results demonstrate that the percent of pediatric subjects (10 to <20 kg) falling within the 90% prediction interval of the adult exposure (i.e., 24-hour AUC) was relatively low at 68.4% (as compared to 76.8% and 91.6% for the other pediatric weight bands). As such, approximately 31% of the pediatric subjects of 10 to <20 kg are projected to have exposures lower than the 5th percentile of the reference adult exposure ([Figure 3](#)).

In regard to the exposure-matching approach, the Applicant used the adult subjects as the reference exposure; however, the review team considers the 20 to <55 kg pediatric subgroup to be more similar to those weighing 10 to <20 kg based on physiology, disease state, and disease progression. Furthermore, the review team assessed efficacy in these pediatric subgroups in the phase 3 clinical trials and found the pediatric subgroup of 20 to <55 kg to be an acceptable efficacy reference group for exposure matching for the 10 to <20 kg group based on the percent change from baseline in glucocorticoid dose and proportion of subjects achieving a glucocorticoid dose ≤ 11 mg/m²/day at Week 28 ([Table 30](#)).

Based on popPK modeling and simulation, the proposed 25 mg bid dosing regimen for the 10 to <20 kg pediatric subgroup is expected to produce similar exposures to those of 50 mg bid for the 20 to <55 kg pediatric subgroup, and therefore, efficacy is expected to be similar between these two pediatric subgroups. Additionally, the relatively higher exposure in adult subjects serves as an appropriate safety exposure coverage. Overall, the exposures of the proposed 25 mg bid dosing regimen in the 10 to <20 kg pediatric subgroup is expected to be safe and effective. Refer to Section [20.5](#) for details on exposure comparison and matching.

Table 30. Pediatric Subgroup Efficacy Analysis Results by Weight Band, Trial NBI-74788-CAH2006

Efficacy Endpoint (Placebo-Subtracted Difference)	20 - <55 kg (n=51)	≥55 kg (n=52)	Overall (n=103)
Percent CFB in GC dose at Week 28 (LS mean difference)	-25.3%	-22.7%	-23.5%
Proportion achieving GC dosing ≤11 mg/m ² /day at Week 28	37%	22%	30%
CFB in A4 level at Week 4 (LS mean difference, ng/dL)	-196.7	-323.5	-268
CFB in 17-OHP level at Week 4 (LS mean difference, ng/dL)	-4626	-7862	-6421

Source: clinical reviewer-generated based on the Applicant's analysis

20-<55 kg weight band (37 crinecerfont, 14 placebo), ≥55 kg weight band (32 crinecerfont, 20 placebo), overall (69 crinecerfont, 34 placebo)

Abbreviations: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; CFB, change from baseline; GC, glucocorticoid; LS, least-squares

Conclusion

The Applicant's proposed dosage of 25 mg twice daily for pediatric patients weighing 10 kg to less than 20 kg is acceptable.

13. Safety (Risk and Risk Management)

13.1. Potential Risks or Safety Concerns Based on Nonclinical Data

The safety of crinecerfont was evaluated in nonclinical safety pharmacology studies, subchronic and chronic toxicology studies in rats and dogs, reproductive and developmental studies in rats and rabbits, genetic toxicology studies, juvenile studies in rats, and 2-year rat and 6-month transgenic mouse carcinogenicity studies. Systemic steady-state crinecerfont exposures increased with dose in a less than dose-proportional manner and approached or reached saturation in the pivotal nonclinical studies. Maximum plasma exposures declined after repeated dosing, likely as a result of induced liver drug-metabolizing enzymes, which contributed to the saturation of exposure observed in the toxicity studies. Thus, clinical exposure multiples at the no-observed-adverse-effect levels (NOAELs) in the pivotal nonclinical studies were limited to one- to fourfold the maximum recommended human dose (MRHD). Nonclinical data relevant to clinical risk assessment or safety concerns are discussed below (see Section 19 for the detailed nonclinical assessment). Overall, nonclinical data support the safe use of crinecerfont for the indicated patients with CAH ≥4 years old.

Safety Pharmacology

Crinecerfont administered as a single oral or IV dose had no significant effects on neurobehavioral function in rats, cardiovascular function in dogs, respiratory function in guinea pigs, renal function in rats, or gastrointestinal function in rats at clinically relevant doses. Crinecerfont showed no potential for clinical arrhythmia risk in vitro in human ether-à-go-go-related gene (hERG) current (<5% inhibition at 10μM) or isolated rabbit Purkinje fiber action

potential. Overall, the safety pharmacology data demonstrated that crinecerfont did not pose acute safety concerns at clinically relevant exposure levels.

General Toxicology

The toxicity of crinecerfont was evaluated in a series of single- and repeat-dose studies in mice, rats, and dogs. The target organs for crinecerfont were liver (mouse, rat, and dog), thyroid gland (rat and dog), gastrointestinal (GI) tract (mouse and rat), and coagulation-associated effects. GI tract findings were not clinically relevant and thyroid gland findings are discussed in the context of carcinogenic potential (below). Clinical trial data identified neutropenia and neuropsychiatric safety as potential clinical risks. Neutropenia was not observed in the pivotal rat or dog toxicity studies and there were no nonclinical signals for immunosuppression or neurobehavioral effects. Mechanistic studies showed crinecerfont is active at the pituitary and can cross the blood-brain barrier, but distribution to the central nervous system was low, with an observed brain to plasma ratio of 0.1. In comparison, crinecerfont was highly distributed to liver (where it is metabolized) as evidenced by a ≥ 8.5 liver-to-plasma ratio.

Initial studies with a crinecerfont tosylate formulation were associated with coagulopathy (prolongation of prothrombin time [PT] and activated partial thromboplastin time [APTT] and/or bleeding) and mortality in repeat-dose rat studies. Subsequently, the tosylate salt formulation was replaced with a free base form of crinecerfont for evaluation in the pivotal chronic toxicology, carcinogenicity, prenatal and postnatal and juvenile nonclinical studies, and for the clinical studies. In chronic rat studies with crinecerfont free base, no mortality or bleeding effects were noted; however, changes in coagulation parameters (prolongation of PT up to 60%, and APTT up to 90%) were observed at 1250 mg/kg/day (6-fold MRHD exposure). Similar findings (prolongation of PT) were observed in the chronic dog study conducted with crinecerfont free base, without any other coagulopathy up to 1000 mg/kg/day (5-fold MRHD exposure). (b) (4)

. Drug-related effects on coagulation were routinely monitored in clinical trials with the crinecerfont free base formulation.

Crinecerfont is predominantly metabolized by CYP3A4 in the liver in animals and in humans. In rats and dogs, crinecerfont induces drug-metabolizing enzymes, which resulted in increased liver weight and hepatocellular hypertrophy in both species. Mechanistic studies confirmed that induction of metabolizing enzymes contributed to dose- and duration-dependent signs of liver toxicity. In rodents only, higher crinecerfont doses (approximately seven times MRHD exposures) caused a low incidence of more advanced liver injury, including multinucleated hepatocytes and anisokaryosis and minimal hepatocyte necrosis. There were no liver findings of concern at doses corresponding to one- to fourfold clinical exposures, and induction or inhibition of liver metabolizing enzymes is unlikely to occur at clinically relevant doses. Routine monitoring for biomarkers and signs of drug-induced liver injury was conducted throughout the clinical development program.

Reproductive, Developmental, and Juvenile Toxicology

The effects of crinecerfont on fertility, reproduction, early embryonic and embryo-fetal development, and juvenile development were evaluated in rat and rabbit toxicology studies. Investigations with the crinecerfont tosylate salt did not identify effects on male or female

fertility or early embryonic development at low clinical exposure margins (two- to fourfold clinical MRHD exposures).

There were also no effects of crinecerfont on rat embryo-fetal development, pre- and postnatal development, or juvenile development that raised concerns about clinical safety. Exposure was limited by tolerability in the rat studies, reaching approximately four times maximum clinical exposure. The toxicity profile of crinecerfont in juvenile rats was comparable to the adult toxicity profile. Juvenile animal findings support the safety of crinecerfont in the indicated pediatric patients ≥ 4 years of age.

In the embryo-fetal development study in rabbits, there were multiple craniofacial malformations in a few fetuses, from multiple litters, which were not present in the concurrent control and were outside the historical control range. The malformations included microcephaly, microstomia, acephalostomia, misshapen cerebrum and/or cerebellum, among others. Exposure attained in the rabbit study ranged between $2\times$ to $3\times$ MRHD, without a dose dependency, despite a 10-fold increase in nominal dose (100 mg/kg low dose to 1000 mg/kg high dose), indicating saturation of absorption. The absence of a dose-related increase in exposure confounds identification of an exposure/response relationship on embryo-fetal development. We therefore assessed the incidence of malformations across all treatment groups because of the similar crinecerfont exposures—there were 4 fetuses from four litters with craniofacial poly-malformations of interest, for a total fetal incidence of 0.8% (4/525) in 7% (4/59) of litters. These specific findings were not present in the historical control data from the same study site. The overall incidence of fetal malformations was low and there was no clear relationship to drug, but absent similar findings in concurrent control fetuses, and with the incidence being outside the historical control range for individual malformations, we cannot rule out a possible effect of crinecerfont treatment on rabbit embryo-fetal development. Rabbit findings and potential implications for clinical risk of special populations will be addressed in labeling.

Additional details of the developmental, reproductive, and juvenile development toxicity studies can be found in Section [19](#). A discussion of the developmental and reproductive toxicology data relevant to crinecerfont use in pregnant people can be found in Section [14.4](#).

Carcinogenicity

The oncogenic potential of crinecerfont was evaluated in two-year rat and 6-month transgenic mouse carcinogenicity studies. Crinecerfont did not show oncogenic effects in transgenic mice. In the 2-year rat study, crinecerfont increased the incidence of thyroid gland follicular cell adenoma and carcinoma in females at 100 mg/kg crinecerfont (4-fold MRHD exposure). Thyroid gland follicular cell tumors arise from excessive clearance of thyroid hormone from induction of liver drug-metabolizing enzymes, which results in release of, and continuous stimulation by, thyroid stimulating hormone (TSH) on the thyroid follicular cells. This mechanism of inducing thyroid gland follicular cell hyperplasia and subsequent tumor development in rats is considered not relevant in humans ([Wu and Farrelly 2006](#); [Bartsch et al. 2018](#)). Additional evidence from the chronic 6-month rat toxicity study showed increased thyroid gland weights and follicular cell hypertrophy and hyperplasia, with increased TSH measured in the subchronic rat study further supporting thyroid hormone stimulation leading to thyroid gland hypertrophy. Overall, the data from genotoxicity, 6-month transgenic mouse carcinogenicity, and two-year rat carcinogenicity studies show that the potential human oncogenic risk of crinecerfont is low.

13.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Crinecerfont is a first-in-class drug, so there is no marketing experience. Adrenal insufficiency was identified as a potential safety concern because of the drug's mechanism of action. Crinecerfont decreases pituitary ACTH levels, leading to decreased adrenal androgen levels, and ultimately allowing for reduction in glucocorticoid dosage.

Neuropsychiatric safety was identified as another potential concern because crinecerfont is centrally acting and was previously in development as a treatment for major depression.

Potential risks of hypersensitivity and neutropenia were identified because of observations in earlier clinical studies. A hypersensitivity event of angioedema occurred in a phase 1 study (Study NBI-74788-1724) of two dose regimens of crinecerfont (100 mg qAM/200 mg qPM, or 100 mg qAM/150 mg qPM) in healthy adult volunteers. According to the Applicant, the 41-year-old male with no relevant past medical history developed a moderate-grade generalized rash after 3 days of crinecerfont treatment with 100/150 mg. He subsequently experienced perioral edema and throat tightness. No symptoms of shortness of breath or difficulty swallowing were reported, and vital signs were stable. These signs and symptoms resolved following treatment with dexamethasone, inhaled epinephrine, and an oral corticosteroid taper. The study drug was discontinued because of the hypersensitivity event. The investigator considered the event possibly related to study drug. Hypersensitivity reactions are discussed further in Section [13.7.2](#).

Neutropenia was observed in a phase 2 study of crinecerfont for major depressive disorder (Study DFI5687). There was a higher incidence of transient low neutrophil counts ($<1.5 \times 10^3$ cells/ μ L for non-Black subjects, $<1 \times 10^3$ cells/ μ L for lack subjects) in the crinecerfont 100 mg group (12.9%) compared with the placebo and escitalopram groups (3.5% and 6.1%, respectively) in this study. Neutropenia is discussed further in Section [13.7.3](#).

13.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Not applicable. The drug is not marketed in any country.

13.4. FDA Approach to the Safety Review

The phase 3 trials, CAH3003 (conducted in adults with CAH) and CAH2006 (conducted in children aged 4 years to 17 years with CAH), were used to support the safety review. The Applicant's safety analysis included results of the completed 6-month double-blind treatment period for both studies and the subset of available data from ongoing open-label periods through Month 12 for Trial CAH3003 (data cutoff July 19, 2023) and Week 52 for Trial CAH2006 (data cutoff August 9, 2023). The Applicant subsequently submitted the completed 120-day Safety Update (data cutoff January 16, 2024, for Trial CAH3003 and February 6, 2024, for Trial CAH2006), which was incorporated into the safety review and included data from the open-label extension (post-Month 12). We present the safety data from each distinct period (i.e., 24-week double-blind treatment period, open-label treatment Months 6 to 12, followed by open-label

extension post-Month 12), with the safety analysis focusing on data from the 24-week placebo-controlled treatment periods.

The Applicant defined the double-blind period safety analysis set as all randomized subjects who took at least one dose of study treatment during the double-blind, placebo-controlled period. The Applicant defined the open-label period safety analysis set as all subjects who took at least one dose of crinecerfont during the open-label period.

Treatment-emergent adverse events (TEAEs) were protocol-defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug plus 28 days. Laboratory, electrocardiogram, or physical examination findings that were considered clinically significant in the opinion of the investigator could be considered adverse events. All AEs in the reviewed trials were graded by investigators using a three-category intensity scale, shown in [Table 31](#), with options of mild, moderate, or severe, which was reviewed and found to be acceptable.

Table 31. Adverse Events Rating Scale Used in Phase 3 Trials NBI-74788-CAH2006 and NBI-74788-CAH3003

Grade	Intensity
Mild	An adverse event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Moderate	An adverse event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort, but poses no significant or permanent risk of harm to the research participant.
Severe	An adverse event that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

Source: Table 3, p. 62 protocol CAH3003

We performed an independent analysis of the adverse events in the safety analysis dataset. The data were analyzed by individual trial with focus on the double-blind placebo-controlled period. AE data are presented by trial period:

- Double-blind treatment period (baseline to Week 24 for Trial CAH3003 and baseline to Week 28 for Trial CAH2006)
- Open-label treatment period (Weeks 24/28 to Weeks 48/52)
- Open-label extension (Month 12 forward)

Laboratory and vital sign data are summarized for the double-blind treatment period only, except in the event of a safety signal which would prompt additional examination of the subsequent treatment periods. Laboratory abnormalities were categorized by severity according to the FDA Standard Safety Tables and Figures: Integrated Guide.⁷

No major data quality or integrity issues were identified that would preclude performing a safety review for this NDA. There were no major identified issues with respect to recording, coding,

⁷ Center for Drug Evaluation and Research (CDER) Biomedical Informatics and Regulatory Review Science (BIRRS) Team, FDA Standard Safety Tables and Figures: Integrated Guide, October 2021.

and categorizing adverse events. The Applicant's translations of verbatim terms to MedDRA (Medical Dictionary for Regulatory Activities) preferred terms for the events reported in Trials CAH3003 and CAH2006 were reviewed and found to be acceptable.

13.5. Adequacy of the Clinical Safety Database

Incorporating the two pivotal phase 3 studies, the safety database is adequate for the proposed CAH indication, dosage regimens, and patient population. Total exposure to crinecerfont in both trials was 216 person-years, with 134 person-years in Trial CAH3003 and 82 person-years in Trial CAH2006. The majority of subjects in both trials completed the full one-year treatment period. A total of 179 subjects were exposed to crinecerfont for ≥ 46 weeks in the two trials combined. Extent of exposure in each phase 3 trial is shown in [Table 32](#) and [Table 33](#), respectively. The exposure is adequate to evaluate the safety of chronic use.

Table 32. Duration of Exposure, Safety Population, Trial NBI-74788-CAH3003

Parameter	Crinecerfont (DB) to Crinecerfont (OL) Weeks 24 to 48 N=117	Placebo (DB) to Crinecerfont (OL) Weeks 24 to 48 N=57	Crinecerfont (DB) to Crinecerfont (OL) Day 1 to Week 48 N=122
Duration of treatment, weeks			
Mean (SD)	23.6 (3.2)	23.9 (3.1)	46.3 (8.1)
Median (Q1, Q3)	24.1 (23.1, 24.6)	24.1 (23.1, 25)	48.1 (47.4, 48.7)
Min, max	1.6, 27.7	7.6, 32.4	2.6, 51.9
Total exposure (person years)	53	26	108
Subjects treated, by duration, n (%)			
<4 weeks	1 (0.9)	0	1 (0.8)
≥ 4 to <12 weeks	2 (1.7)	1 (1.8)	2 (1.6)
≥ 12 to <18 weeks	1 (0.9)	1 (1.8)	1 (0.8)
≥ 18 to <22 weeks	0	1 (1.8)	0
≥ 22 to <26 weeks	102 (87.2)	48 (84.2)	1 (0.8)
≥ 26 to <30 weeks	11 (9.4)	5 (8.8)	1 (0.8)
≥ 30 to <36 weeks	0	1 (1.8)	2 (1.6)
≥ 36 to <42 weeks	0	0	1 (0.8)
≥ 42 to <46 weeks	0	0	0
≥ 46 to <50 weeks	0	0	102 (83.6)
≥ 50 to <52 weeks	0	0	11 (9.0)
≥ 52 weeks	0	0	0

Source: adsl.xpt; Software: R

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont 100 mg twice daily in the double-blind treatment period and continued on crinecerfont 100 mg twice daily in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont 100 mg twice daily in the open-label treatment period.

Duration is 24 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Abbreviations: DB, double-blind; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; OL, open-label; Q1, first quartile; Q3, third quartile; SD, standard deviation

Table 33. Duration of Exposure, Safety Population, Trial NBI-74788-CAH2006

Parameter	Crinecerfont (DB) to Crinecerfont (OL) Weeks 28 to 52 N=66	Placebo (DB) to Crinecerfont (OL) Weeks 28 to 52 N=31	Crinecerfont (DB) to Crinecerfont (OL) Day 1 to Week 52 N=69
Duration of treatment, weeks			
Mean (SD)	24.2 (1.4)	24.1 (1.2)	51.2 (5.2)
Median (Q1, Q3)	24.1 (23.9, 24.8)	24.1 (23.5, 24.6)	52.1 (51.6, 52.4)
Min, max	20, 29.3	21.1, 28.1	27.3, 58.1
Total exposure (person years)	31	14	68
Subjects treated, by duration, n (%)			
<4 weeks	0	0	0
≥4 to <12 weeks	0	0	0
≥12 to <18 weeks	0	0	0
≥18 to <22 weeks	3 (4.5)	1 (3.2)	0
≥22 to <26 weeks	58 (87.9)	29 (93.5)	0
≥26 to <30 weeks	5 (7.6)	1 (3.2)	3 (4.3)
≥30 to <36 weeks	0	0	0
≥36 to <42 weeks	0	0	0
≥42 to <46 weeks	0	0	0
≥46 to <50 weeks	0	0	0
≥50 to <52 weeks	0	0	21 (30.4)
≥52 to <54 weeks	0	0	42 (60.9)
≥54 weeks	0	0	3 (4.3)

Source: adsl.xpt; Software: R

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 28 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Abbreviations: DB, double-blind; N, number of subjects in treatment arm; n, number of subjects with given treatment duration; OL, open-label; Q1, first quartile; Q3, third quartile; SD, standard deviation

13.6. Safety Results

13.6.1. Safety Results, Pooled Analyses, Trials CAH3003 and CAH2006

Not applicable. Trials CAH3003 and CAH2006 are reviewed separately because of different subject populations (adults versus pediatric subjects), study designs, and crinecerfont doses.

13.6.2. Safety Results, Trial CAH3003

13.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Trial CAH3003

13.6.2.1.1. Double-Blind Treatment Period

During the double-blind placebo-controlled treatment period of Trial CAH3003, the overall rates of any adverse event were similar in the crinecerfont (83%) compared to the placebo (81%) group ([Table 34](#)). Serious adverse events and adverse events leading to permanent discontinuation of study drug were more common in the crinecerfont group than in placebo. The 95% confidence interval for the risk difference between the crinecerfont and placebo group in these adverse event categories crossed zero, so differences were not significantly different. However, the trial was not designed nor powered to determine a statistically significant difference in adverse event rates.

Table 34. Overview of Adverse Events, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Event Category	Crinecerfont N=122 n (%)	Placebo N=59 n (%)	Risk Difference % (95% CI)
Any AE	101 (82.8)	48 (81.4)	1.4 (-9.8, 14.6)
SAE	4 (3.3)	0	3.3 (-2.9, 8.1)
AE leading to permanent discontinuation of study drug	4 (3.3)	0	3.3 (-2.9, 8.1)
AE leading to interruption of study drug	6 (4.9)	3 (5.1)	-0.2 (-9.4, 6.3)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

13.6.2.1.2. Open-Label Treatment Period (Weeks 24 to 48)

The overall rate of any adverse event decreased from 81% in the placebo double-blind (DB) period to 70% during the open-label period in the placebo/crinecerfont group and decreased from 83% in the crinecerfont DB period to 62% during the open-label period in the crinecerfont/crinecerfont group ([Table 35](#)). During the open-label treatment phase, the rates of serious AEs did not increase significantly (3% to 4%) in subjects who remained on crinecerfont. Subjects who transitioned from placebo during the DB phase to crinecerfont experienced an increase in serious AE incidence from zero to 5% as shown in [Table 35](#).

Table 35. Overview of Adverse Events, Safety Population, Trial NBI-74788-CAH3003, Open-Label and Double-Blind Treatment Periods

Event Category	Crinecerfont (DB) to Crinecerfont (OL) Weeks 24 to 48 N=117 n (%)	Crinecerfont (DB) Period Weeks 0 to 24 N=122 n (%)	Placebo (DB) to Crinecerfont (OL) Weeks 24 to 48 N=57 n (%)	Placebo (DB) Period Weeks 0 to 24 N=59 n (%)
Any AE	73 (62.4)	101 (82.8)	40 (70.2)	48 (81.4)
SAE	5 (4.3)	4 (3.3)	3 (5.3)	0
AE leading to permanent discontinuation of study drug	2 (1.7)	4 (3.3)	0	0
AE leading to interruption of study drug	4 (3.4)	6 (4.9)	1 (1.8)	3 (5.1)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 24 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; DB, double-blind; N, number of subjects in treatment arm; n, number of subjects with at least one event; OL, open-label; SAE, serious adverse event

13.6.2.1.3. Open-Label Extension (Month 12 Onward)

All 167 subjects who completed the open-label treatment period continued into the open-label extension. The safety analysis in the ongoing open-label extension includes data from 117 subjects who were not rerandomized at Month 12. The 50 subjects who were rerandomized are not included in the open-label extension safety analysis.

The adverse event rate decreased to 51% in the open-label extension, with the majority of events graded as mild or moderate ([Table 36](#)).

Table 36. Summary of Treatment-Emergent Adverse Events, Trial NBI-74788-CAH3003, Open-Label Extension

Treatment-Emergent Adverse Events	All Subjects N=117 n (%)
Subjects with:	
Any TEAE	60 (51.3)
Any SAE	9 (7.7)
Any TEAE leading to study drug discontinuation	1 (0.9)
Any TEAE resulting in death	1 (0.9)

Source: Safety Update NBI-74788-CAH3003 Table 14.4.1.3.1

Abbreviations: N, number of subjects in analysis; n, number of subjects with adverse event; SAE, serious adverse event; TEAE, treatment-emergent adverse event

13.6.2.2. Deaths, Trial CAH3003

There were no deaths in Trial CAH3003 during the double-blind or open-label treatment periods.

13.6.2.2.1. Open-Label Extension (Month 12 Onward)

One death occurred in a subject on study drug (crinecerfont 100 mg in the morning and 200 mg in the evening) during the open-label extension period. The cause of death was an adrenal crisis. The adrenal crisis was precipitated by an acute infectious illness that was not adequately treated with stress-dose steroids. The death was not likely study-drug-related.

The subject, a 56-year-old male with classic CAH, died during an episode of acute adrenal insufficiency. Approximately 19 months after starting crinecerfont and 15 months after achieving a lower glucocorticoid dose of 9.8 mg/m²/day hydrocortisone equivalent, he developed a flu-like illness with nausea, vomiting, and lethargy. He had recently been exposed to visiting family members with similar symptoms. The following day, he vomited 3 times. That evening, he informed his visiting family members that he would start stress dosing of steroids with his next glucocorticoid dose and was going to bed. He was found dead on the floor the next morning. Autopsy findings showed inflammatory infiltrates in his lungs consistent with his reported flu-like syndrome, and cardiomegaly and hepatomegaly thought to be related to his uncontrolled diabetes.

13.6.2.3. Serious Treatment-Emergent Adverse Events, Trial CAH3003

13.6.2.3.1. Double-Blind Treatment Period

The overall rate of serious TEAEs during the 24-week double-blind treatment period of Trial CAH3003 was 3.3% (in four subjects) in the crinecerfont group and none in the placebo group ([Table 37](#)).

Four subjects experienced serious TEAEs during the double-blind treatment period. One event was presyncope, the cause of which is unclear, but did not recur despite resuming study drug:

- Presyncope occurred in a 48-year-old female who developed fatigue, general malaise, and myalgias on Study Day 64 (Week 9, during the glucocorticoid reduction period) and was admitted to the hospital for evaluation. Her glucocorticoid dose was decreased from 14.5 mg/m²/day at baseline to 11.6 mg/m²/day at Week 6 and she remained at a dose of 11.6 mg/m²/day at Week 9. The evaluation was unremarkable, without orthostatic hypotension or laboratory signs of adrenal insufficiency. She was successfully treated with intravenous fluids, electrolytes, and hydrocortisone. Study drug was interrupted for 1 day and she continued study drug into the open-label treatment period with no recurrence of presyncope.

The three remaining serious TEAEs occurring during the double-blind treatment period are not likely study-drug-related:

- A serious adverse event (SAE) of acute adrenocortical insufficiency during the double-blind treatment period occurred in a 24-year-old female. Concomitant medications administered within 30 days before the event included fludrocortisone and hydrocortisone. On Day 30, the subject experienced vomiting for which she self-administered emergency hydrocortisone. Her glucocorticoid dose at Week 4 was 16 mg/m²/day hydrocortisone equivalents, which had not changed from baseline.

Symptoms persisted and the subject was admitted to the hospital on Study Day 33 for vomiting and tachycardia. Laboratory evaluation revealed signs of adrenal insufficiency (hyponatremia and an elevated plasma renin activity). After admission, the subject developed a cough with elevated white blood count, was diagnosed with a lower respiratory infection, and treated with doxycycline. Her adrenal insufficiency was successfully treated with intravenous hydrocortisone, fluids, and an antiemetic.

Study drug was interrupted for 11 days during her recovery, after which she resumed crinecerfont, completed the double-blind treatment period, and then continued into the open-label treatment period.

The SAE of acute adrenal insufficiency was considered the result of lower respiratory tract infection and not due to study drug. This reviewer concurs with that assessment.

- An SAE of acute cholecystitis occurred on study treatment Day 166 in a 48-year-old transgender female with obesity who was assigned to crinecerfont 100 mg twice daily. Concomitant medications included estradiol. The subject was hospitalized and treated with intravenous antibiotics with full recovery. No change was made to crinecerfont therapy. The subject's history of obesity and treatment with estradiol increased her risk of developing gallstones and subsequently, cholecystitis.
- An 18-year-old female with a history of acne experienced SAEs of cellulitis and groin abscess on Study Day 142 (Week 20). At the Week 12 study visit, routine laboratory testing showed white blood cell and neutrophil counts within the normal range. The abscess was treated with antibiotics, incision, and drainage, and was not likely study-drug-related. No changes to the study drug treatment were made. The investigator considered the SAEs unlikely to be related to study drug. The subject completed the double-blind period and continued into the open-label treatment phase.

Table 37. Subjects With Serious Adverse Events by Preferred Term, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Preferred Term	Crinecerfont N=122 n (%)	Placebo N=59 n (%)	Risk Difference % (95% CI)
Any SAE	4 (3.3)	0	3.3 (-2.9, 8.1)
Adrenocortical insufficiency acute	1 (0.8)	0	0.8 (-5.3, 4.5)
Cholecystitis acute	1 (0.8)	0	0.8 (-5.3, 4.5)
Cellulitis	1 (0.8)	0	0.8 (-5.3, 4.5)
Groin abscess	1 (0.8)	0	0.8 (-5.3, 4.5)
Presyncope	1 (0.8)	0	0.8 (-5.3, 4.5)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event

13.6.2.3.2. SAEs During Open-Label Treatment Period (Weeks 24 to 48)

[Table 38](#) shows the serious TEAEs that began during the open-label treatment period according to treatment received in the double-blind phase (i.e., placebo or crinecerfont). There were nine events in eight subjects. Acute adrenal insufficiency was the only preferred term that occurred in more than one subject.

The events (preferred terms) of tympanic membrane perforation, gastroenteritis viral, coronavirus infection, and Bell's palsy are considered unrelated to study drug due either to identification of an alternate cause, or unlikely relationship to pharmacology of crinecerfont. The event of joint injury was a case of right knee torsion injury sustained during a skateboarding accident.

The two cases of adrenocortical insufficiency were both preceded by acute infection accompanied by vomiting. In one of the two cases, the subject had been unable to take stress-dose steroids due to vomiting. Both events were attributed to infection and not considered related to study drug.

There was a serious AE of suicide attempt, for which a drug effect cannot be excluded:

- The serious adverse event of suicide attempt involved a 29-year-old female with a history of acne who had received crinecerfont 100 mg bid starting in the double-blind treatment period and continuing during the open-label treatment period. Concomitant medications administered within 30 days of the event included hydrocortisone and paracetamol/tramadol.

On Study Day 320 (also Day 320 of study drug administration), she was hospitalized after taking 19 tramadol tablets and thiocodin as well as intentionally injuring her arm. Three days prior to hospital admission she had ended a seven-year romantic relationship and experienced significant deterioration of her mental condition. Computed tomography scanning showed cortical brain atrophy. Study drug was discontinued because of the suicide attempt. The investigator considered the suicide attempt to be unrelated to study treatment.

The remaining SAE described below, was not considered related to study drug following review of the narrative:

- A 46-year-old male had an anaphylactic reaction to tree nuts. He had a history of a tree nut allergy and ate cake containing nuts on Study Day 332 during the open-label treatment period. He was treated with antihistamine and hydrocortisone in the emergency department with resolution the same day. He continued on study drug after the event. This SAE was not drug-related.

Table 38. Subjects With Serious Adverse Events by Preferred Term, Safety Population, Trial NBI-74788-CAH3003, Open-Label Treatment Period (Weeks 24 to 48)

Preferred Term	Crinecerfont (DB) to Crinecerfont (OL) Weeks 24 to 48 N=117 n (%)	Placebo (DB) to Crinecerfont (OL) Weeks 24 to 48 N=57 n (%)
Any SAE	5 (4.3)	3 (5.3)
Tympanic membrane perforation	1 (0.9)	0
Adrenocortical insufficiency acute	1 (0.9)	1 (1.8)
Anaphylactic reaction	0	1 (1.8)
Coronavirus infection	1 (0.9)	0
Gastroenteritis viral	0	1 (1.8)
Joint injury	1 (0.9)	0
Bell's palsy	1 (0.9)	0
Suicide attempt	1 (0.9)	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 24 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Abbreviations: DB, double-blind; N, number of subjects in treatment arm; n, number of subjects with adverse event; OL, open-label; SAE, serious adverse event

13.6.2.3.3. Serious Adverse Events Reported in Open-Label Extension (Month 12 Onward)

Nine subjects experienced serious adverse events in the open-label extension through the data cutoff date of the 120-day safety update submission ([Table 39](#)). There were three cases of acute adrenocortical insufficiency, one of which was fatal and is described in Section [13.6.2.2.1](#) above.

Review of this narrative and the other nonfatal cases of acute adrenocortical insufficiency do not suggest a relationship to crinecerfont treatment. All events except one were preceded by acute illness and associated with inadequate stress dosing of steroids. The remaining event involved a 52-year-old male who was hospitalized for vomiting and hypoxia. He reported an antecedent history of several months of generalized weakness and chronic diarrhea. Hospital evaluation yielded no evidence of underlying infection, and no unifying diagnosis was made. However, the subject's symptoms improved with stress-dose steroids, and he resumed crinecerfont without recurrence of symptoms. The cause of adrenal insufficiency in this subject is unclear but could relate to dehydration from chronic diarrhea, or to a subacute non-bacterial infectious or other inflammatory etiology. Negative rechallenge with study drug suggests the event was not related to crinecerfont.

The remaining narratives for SAEs were reviewed and there is no suggestion that the events were related to study drug, as events resolved while the subjects continued on crinecerfont and/or an alternative etiology was identified.

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

Table 39. Serious Adverse Events, Open-Label Extension (Month 12 Onward), Trial NBI-74788-CAH3003

Treatment Group	Age/Sex/Race	MedDRA Preferred Term	Event Study Day Start/Stop**	Investigator Assessment of Relationship to Study Drug	Recovered/Resolved	Crinecerfont Continued During/After AE
Crinecerfont 200/100	56/Male/White	Adrenocortical insufficiency acute	740-740	Unlikely	Fatal	N/A
Crinecerfont 100 mg bid	52/Male/Native	Gastroenteritis	427-431	Unlikely	Yes	Yes
		Adrenocortical insufficiency acute ^a	963-965	Unlikely	Yes	Yes
Crinecerfont 100 mg bid	42/Female/White	Cholelithiasis	402-429	Unlikely	Yes	Yes
Crinecerfont	30/Female/Multiple	Gastroenteritis, pelvic inflammatory disease, dehydration, sepsis	462-473	Not related	Yes	Yes
Crinecerfont	32/Male/White	Gastroenteritis viral	450-453	Unlikely	Yes	Yes
Crinecerfont 100 mg bid	46/Female/White	Vertigo ^b	513-ongoing	Not related	No	Yes
Crinecerfont 100 mg bid	22/Male/White	Loss of consciousness ^c	442-442	Unlikely	Yes	yes
Crinecerfont	27/Male/White	Adrenocortical insufficiency acute	338-342	Not related	Yes	
Crinecerfont 100 mg bid	33/Male/White	Gastroenteritis norovirus	375-376	Not related	Yes	Yes

Source: Modified from Applicant's submitted Safety Update Report, Table 20, p40

** Relative to Study Day 1

^a Presented with nausea, vomiting, and hypoxia. Antecedent history of several months of generalized weakness and chronic diarrhea. No evidence of underlying infection and no unifying diagnosis made.

^b Patient diagnosed with peripheral vestibular hypofunction due to vestibular neuritis.

^c The etiology is unclear. No evidence of epilepsy. The work-up was unrevealing.

Abbreviations: AE, adverse event; bid, twice daily; MedDRA, Medical Dictionary for Regulatory Activities; N/A, not applicable

13.6.2.4. Adverse Events Leading to Treatment Discontinuation, Trial CAH3003

13.6.2.4.1. Double-Blind Treatment Period

A total of four subjects (3.3%) in the crinecerfont group and none in the placebo group experienced an adverse event leading to study drug discontinuation during the double-blind treatment period ([Table 40](#)). No single preferred term occurred in more than one subject.

During the double-blind treatment period, adverse events of restlessness, apathy, dyspepsia, nausea, and vomiting, involving two subjects described below, are possibly study-drug-related:

- A 28-year-old male developed restlessness on Study Day 3 and apathy on Study Day 54. He also had an increase in his Columbia Suicide Severity Rating Scale from 0 to 2 (nonspecific active suicidal thoughts). He discontinued crinecerfont on Study Day 380 during the extended open-label period due to restlessness, with resolution of the restlessness 11 days after discontinuation. The adverse event of restlessness is possibly study-drug-related because crinecerfont is centrally acting and the restlessness resolved after drug discontinuation. Drug-relatedness for apathy and suicidal ideation cannot be excluded.
- Dyspepsia, nausea, and vomiting developed in a 39-year-old female without any noted medical history other than CAH on Study Day 167, which resolved on Study Day 169. She then discontinued study drug on Day 184 due to nausea, vomiting, and dyspepsia. Information is not available regarding resolution of symptoms off study drug.

The adverse events of rash, and gastric ulcer leading to study drug discontinuation are not likely study-drug-related:

- Rash occurred in a 26-year-old female on Study Day 166. She was treated with clobetasol and discontinued the study on Day 589 because of the rash. The rash was still present on Day 671. The rash is not likely study-drug-related because the rash did not resolve after study drug discontinuation.
- Gastric ulcer occurred in a 31-year-old female on Study Day 10. Her medical history included headache, hypertension, menstrual disorder, and sleep apnea. Concomitant medications included hydrocortisone and propranolol. The timing of a gastric ulcer occurring after only 10 days of study drug treatment makes it unlikely to have been related to study drug.

Table 40. Adverse Events Leading to Treatment Discontinuation by Preferred Term, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Preferred Term	Crinecerfont N=122 n (%)	Placebo N=59 n (%)	Risk Difference % (95% CI)
Any AE leading to discontinuation	4 (3.3)	0	3.3 (-2.9, 8.1)
Dyspepsia ^a	1 (0.8)	0	0.8 (-5.3, 4.5)
Gastric ulcer	1 (0.8)	0	0.8 (-5.3, 4.5)
Nausea ^a	1 (0.8)	0	0.8 (-5.3, 4.5)
Vomiting ^a	1 (0.8)	0	0.8 (-5.3, 4.5)
Apathy ^b	1 (0.8)	0	0.8 (-5.3, 4.5)
Restlessness ^b	1 (0.8)	0	0.8 (-5.3, 4.5)
Rash	1 (0.8)	0	0.8 (-5.3, 4.5)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 24 weeks.

^a Dyspepsia, nausea, and vomiting occurred in the same subject

^b Apathy and restlessness occurred in the same subject

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

13.6.2.4.2. Adverse Events Leading to Study Discontinuation During Open-Label Treatment Period (Weeks 24 to 48)

[Table 41](#) shows the AEs leading to study discontinuation that began during the open-label treatment period and are presented according to treatment received in the double-blind phase (i.e., placebo or crinecerfont). There were three events in two subjects.

A suicide attempt occurred during the open-label period and is possibly study-drug-related:

- The serious TEAE of suicide attempt and aggression is described in Section [13.6.2.3.2](#) in a 29-year-old female, which resulted in study drug discontinuation, consistent with study protocol discontinuation criteria. This subject also experienced aggression (self-aggressive behavior). We cannot exclude drug-relatedness for the suicide attempt and self-aggressive behavior because the drug is centrally acting.

The adverse event of urticaria leading to study drug discontinuation is not likely study-drug-related:

- Urticaria occurred in a 48-year-old female on Study Day 197. She discontinued study drug on Day 224 but continued to experience widespread urticaria on Study Day 253, about 1 month after discontinuing the study drug. The urticaria is not likely study-drug-related because the urticaria did not resolve after study drug discontinuation.

Table 41. Adverse Events Leading to Treatment Discontinuation by Preferred Term, Safety Population, Trial NBI-74788-CAH3003, Open-Label Treatment Period

Preferred Term	Crinecerfont (DB) to Crinecerfont (OL) Weeks 24 to 48 N=117 n (%)	Placebo (DB) to Crinecerfont (OL) Weeks 24 to 48 N=57 n (%)
Any AE leading to discontinuation	2 (1.7)	0
Aggression ^a	1 (0.9)	0
Suicide attempt ^a	1 (0.9)	0
Urticaria	1 (0.9)	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 24 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

^a Aggression and suicide attempt occurred in the same subject

Abbreviations: AE, adverse event; DB, double-blind; N, number of subjects in treatment arm; n, number of subjects with adverse event; OL, open-label; SOC, system organ class

13.6.2.4.3. Open-Label Extension (Month 12 Onward)

One subject discontinued study drug during the open-label extension period due to fatal adrenocortical insufficiency as discussed previously in Section [13.6.2.3.3](#).

13.6.2.5. Treatment-Emergent Adverse Events, Trial CAH3003

13.6.2.5.1. Double-Blind Treatment Period

[Table 42](#) lists the adverse events occurring at $\geq 2\%$ frequency in the double-blind treatment period and at a frequency at least 1% greater in the crinecerfont group than in the placebo group.

Fatigue, dizziness, arthralgia, back pain, and decreased appetite are the most common adverse events and may be due to glucocorticoid withdrawal, but a direct effect of crinecerfont itself cannot be excluded. The adverse events of coronavirus infection, rhinitis, and gastroenteritis are not likely study-drug-related based on the mechanism of action of the drug; however, off-target effects cannot be excluded.

Table 42. Common Adverse Events, Safety Population, Occurring at $\geq 2\%$ Frequency and With at Least 1% Greater Frequency in Crinecerfont vs. Placebo Group, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Preferred Term	Crinecerfont N=122 n (%)	Placebo N=59 n (%)	Risk Difference % (95% CI)
Any AE	101 (82.8)	48 (81.4)	1.4 (-9.8, 14.6)
Fatigue	30 (24.6)	9 (15.3)	9.3 (-3.8, 20.6)
Coronavirus infection	17 (13.9)	5 (8.4)	5.5 (-5.6, 14.4)
Dizziness	10 (8.2)	2 (3.4)	4.8 (-4.0, 11.8)
Arthralgia	9 (7.4)	0	7.4 (1.1, 13.4)*
Back pain	7 (5.7)	2 (3.4)	2.3 (-6.3, 8.7)
Blood creatine phosphokinase increased	6 (4.9)	2 (3.4)	1.5 (-7.0, 7.6)
Decreased appetite	5 (4.1)	1 (1.7)	2.4 (-5.2, 7.9)
Gastroenteritis	5 (4.1)	1 (1.7)	2.4 (-5.2, 7.9)
Myalgia	5 (4.1)	1 (1.7)	2.4 (-5.2, 7.9)
Carpal tunnel syndrome	4 (3.3)	1 (1.7)	1.6 (-6.0, 6.8)
Insomnia	4 (3.3)	1 (1.7)	1.6 (-6.0, 6.8)
Rhinitis	3 (2.5)	0	2.5 (-3.7, 7.0)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 24 weeks.

Coded as MedDRA preferred terms.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Myalgia replaces: Pain

Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

13.6.2.5.2. Open-Label Treatment Period (Weeks 24 to 48)

During the open-label treatment period, the rate of any AE decreased from 83% in the crinecerfont DB group to 62% in the crinecerfont/crinecerfont group and decreased from 81% in the placebo DB group to 70% in the placebo/crinecerfont group ([Table 43](#)).

Adverse events occurring in $\geq 4\%$ of subjects in the placebo/crinecerfont group were fatigue, headache, coronavirus infection, nasopharyngitis, diarrhea, dizziness, back pain, and abdominal pain (see [Table 43](#)).

Fatigue, dizziness, arthralgia, back pain, increased creatine phosphokinase (CPK), and decreased appetite all decreased in frequency from the crinecerfont DB period to the crinecerfont/crinecerfont open-label period, suggesting drug tolerance. Overall AE incidence also decreased. These data raise no concerns with respect to the longer-term safety of crinecerfont.

Table 43. Subjects With Adverse Events in the Open-Label Treatment Period, Occurring at ≥4% Frequency, Safety Population, Trial NBI-74788-CAH3003, Double-Blind or Open-Label Treatment Periods

Preferred Term	Crinecerfont (DB) to Crinecerfont (OL) Weeks 24 to 48 N=117 n (%)	Crinecerfont (DB) Period Weeks 0 to 24 N=122 n (%)	Placebo (DB) to Crinecerfont (OL) Weeks 24 to 48 N=57 n (%)	Placebo (DB) Weeks 0 to 24 N=59 n (%)
Any AE	73 (62.4)	101 (82.8)	40 (70.2)	48 (81.4)
Fatigue	9 (7.7)	30 (24.6)	4 (7.0)	9 (15.3)
Headache	10 (8.5)	19 (15.6)	5 (8.8)	9 (15.3)
Coronavirus infection	3 (2.6)	17 (13.9)	4 (7.0)	5 (8.5)
Upper respiratory tract infection	6 (5.1)	11 (9.0)	1 (1.8)	7 (11.9)
Nasopharyngitis	9 (7.7)	6 (4.9)	3 (5.3)	8 (13.6)
Diarrhoea	3 (2.6)	10 (8.2)	4 (7.0)	5 (8.5)
Dizziness	4 (3.4)	10 (8.2)	3 (5.3)	2 (3.4)
Gastroenteritis	7 (6.0)	5 (4.1)	0	1 (1.7)
Arthralgia	1 (0.9)	9 (7.4)	2 (3.5)	0
Myalgia	5 (4.3)	5 (4.1)	2 (3.5)	1 (1.7)
Back pain	3 (2.6)	7 (5.7)	4 (7.0)	2 (3.4)
Blood creatine phosphokinase incr	2 (1.7)	6 (4.9)	0	2 (3.4)
Abdominal pain	3 (2.6)	4 (3.3)	3 (5.3)	2 (3.4)
Decreased appetite	1 (0.9)	5 (4.1)	0	1 (1.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 24 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Coded as MedDRA preferred terms.

Myalgia replaces: Pain

Abbreviations: AE, adverse event; DB, double-blind; incr, increased; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event; OL, open-label

13.6.2.6. Laboratory Findings, Trial CAH3003

See the schedule of assessments in Section [21](#) for the frequency of laboratory monitoring.

Laboratory data for CPK, neutrophil count, and coagulation parameters were examined more closely for the following reasons:

- The adverse event preferred term of blood creatine phosphokinase increased occurred with greater frequency in the crinecerfont versus placebo group (see Section [13.6.2.5](#)).
- A higher incidence of neutropenia was noted in a phase 2 study of crinecerfont in subjects with major depressive disorder (see Section [13.2](#)).
- Nonclinical studies of crinecerfont tosylate formulation were associated with coagulopathy (prolongation of PT and APTT and/or bleeding) and mortality in repeat-dose rat studies. Subsequently, the tosylate salt formulation was replaced with a free base form, which was used for the clinical studies. In chronic rat studies with crinecerfont free base, no mortality or bleeding effects were noted; however, changes in coagulation parameters (prolongation of PT

up to 60%, and APTT up to 90%) were observed at 1250 mg/kg/day (6-fold MRHD exposure). Similar findings (prolongation of PT) were observed in the chronic dog study conducted with crinecerfont free base but without any other coagulopathy up to 1000 mg/kg/day [5-fold MRHD exposure].

13.6.2.6.1. Double-Blind Treatment Period

13.6.2.6.1.1. Chemistry Parameters

Elevated CPK levels occurred more frequently in the placebo group, but CPK levels greater than 5× ULN occurred more frequently in the crinecerfont group. The mean change in CPK levels from baseline over time was slightly higher in the crinecerfont group compared to placebo ([Figure 16](#)).

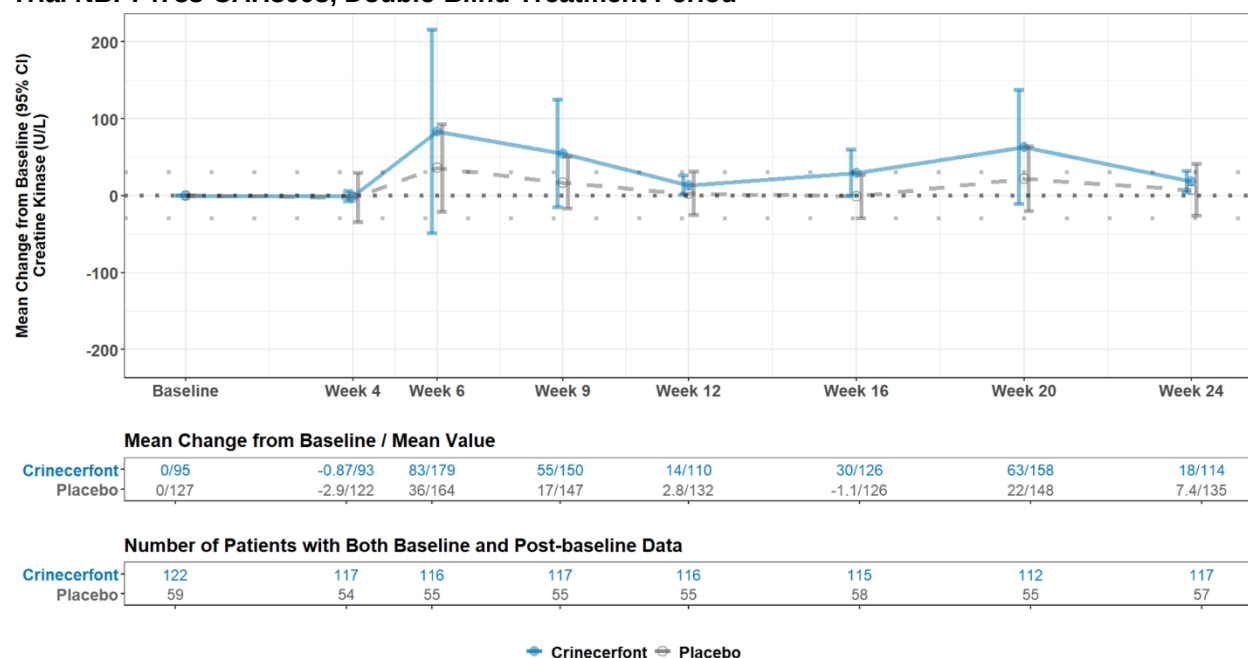
Although more subjects in the placebo group (12%) had CPK levels >3× ULN (Level 1 abnormality) compared to the crinecerfont group (9%), more crinecerfont-treated subjects had CPK values >5× ULN (Level 2 abnormality) and >10× ULN (Level 3 abnormality) than subjects receiving placebo ([Table 44](#)).

Of the five subjects with CPK values >10× ULN (Level 3) in the crinecerfont group during the double-blind treatment period, all elevated levels were documented on a single blood draw and had resolved by the subsequent blood draw. According to the Applicant, most instances of increased CPK levels were associated with significant physical exertion and improved with cessation of the inciting activity. No cases of increased CPK resulted in study treatment discontinuation. There were no reported cases of rhabdomyolysis.

The elevated CPK levels are not likely drug-related because elevated levels >3× ULN occurred more frequently in the placebo group, most instances of elevated CPK levels were explained by other factors, and there is no mechanistic evidence of causality.

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

Figure 16. Mean Creatine Phosphokinase Change From Baseline Over Time, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



Source: adlb.xpt; Software: R
Abbreviations: CI, confidence interval

Table 44. Subjects With Elevated Creatine Phosphokinase Values Meeting Specified Levels, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=122 n/N _w (%)	Placebo N=59 n/N _w (%)	Risk Difference % (95% CI)
CPK, high (U/L)			
Level 1 (>3× ULN)	11/121 (9.1)	7/59 (11.9)	-2.8 (-14.3, 6.1)
Level 2 (>5× ULN)	8/121 (6.6)	0/59 (0)	6.6 (0.3, 12.5)*
Level 3 (>10× ULN)	5/121 (4.1)	0/59 (0)	4.1 (-2.1, 9.3)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

There were no clinically important differences with respect to median change in chemistry parameters (i.e., electrolytes, renal and hepatic function) or incidence of excursions outside the normal range during the double-blind treatment period. Refer to Section 23.2 of this review for summary tables of incidence of chemistry outliers during the double-blind treatment period (Table 195 for chemistry values and Table 196 for renal function values).

Prevalence of abnormal laboratory findings suggestive of adrenal insufficiency (low sodium, high potassium, low glucose, high blood urea nitrogen) were similar between the crinecerfont and placebo groups, with some findings occurring at greater frequency in the placebo group (Table 45).

Table 45. Subjects With Laboratory Excursions Potentially Indicative of Adrenal Insufficiency, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=122 n/N _w (%)	Placebo N=59 n/N _w (%)	Risk Difference % (95% CI)
Sodium, low (mEq/L)			
Level 1 (<132)	12/121 (9.9)	7/59 (11.9)	-1.9 (-13.5, 7.1)
Level 2 (<130)	3/121 (2.5)	5/59 (8.5)	-6.0 (-16.1, 0.4)
Level 3 (<125)	1/121 (0.8)	2/59 (3.4)	-2.6 (-10.8, 1.7)
Potassium, high (mEq/L)			
Level 1 (>5.5)	2/121 (1.7)	2/59 (3.4)	-1.7 (-10.1, 3.1)
Level 2 (>6)	1/121 (0.8)	1/59 (1.7)	-0.9 (-8.3, 3.1)
Level 3 (>6.5)	0/121 (0)	1/59 (1.7)	-1.7 (-9.0, 1.4)
Glucose, low (mg/dL)			
Level 1 (<70)	17/121 (14.0)	10/59 (16.9)	-2.9 (-15.6, 7.7)
Level 2 (<54)	1/121 (0.8)	2/59 (3.4)	-2.6 (-10.8, 1.7)
Level 3 (<40)	1/121 (0.8)	1/59 (1.7)	-0.9 (-8.3, 3.1)
Blood urea nitrogen, high (mg/dL)			
Level 1 (>23)	8/121 (6.6)	5/59 (8.5)	-1.9 (-12.4, 5.8)
Level 2 (>27)	2/121 (1.7)	2/59 (3.4)	-1.7 (-10.1, 3.1)
Level 3 (>31)	1/121 (0.8)	0/59 (0)	0.8 (-5.3, 4.6)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

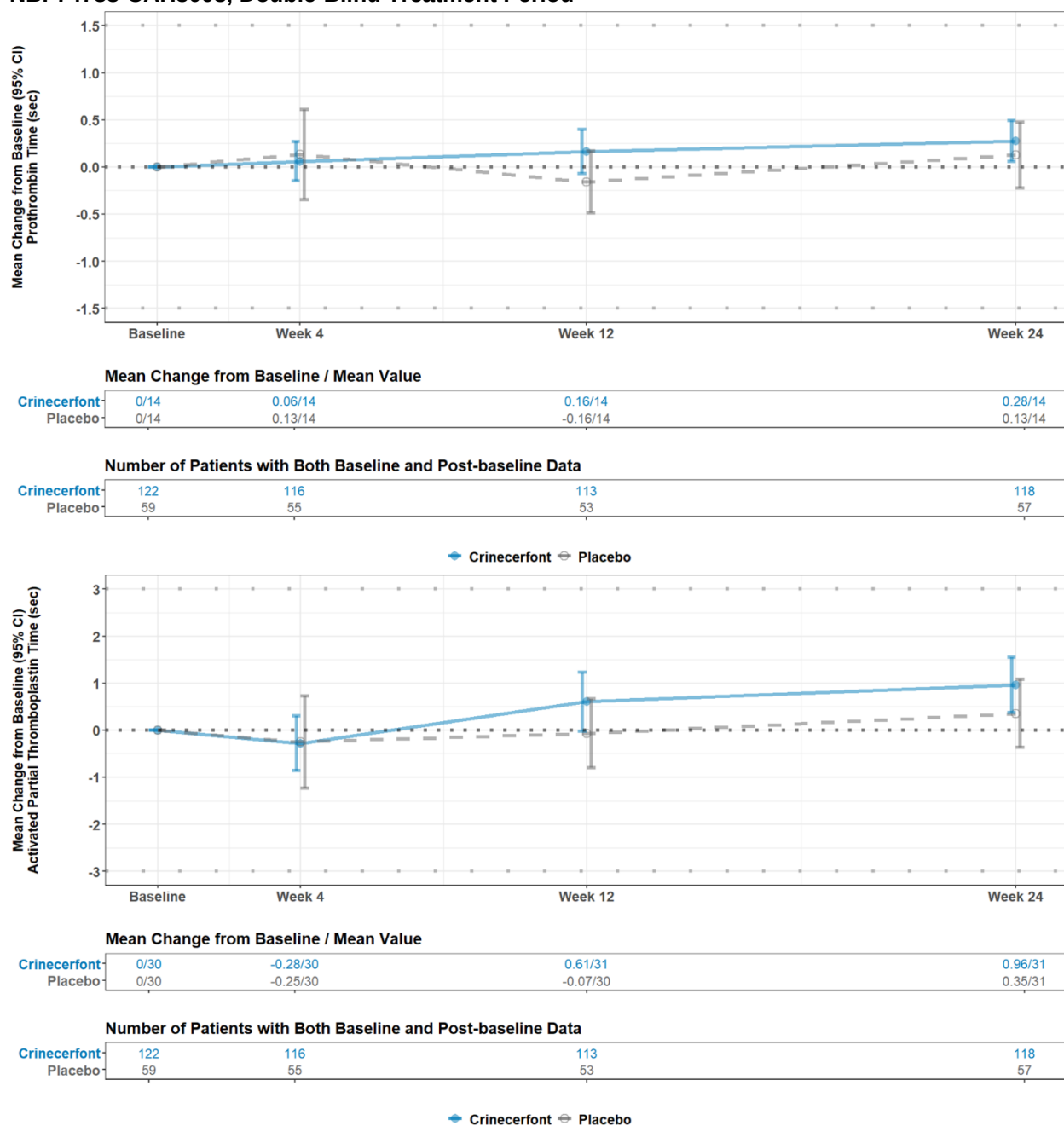
13.6.2.6.1.2. Hematology Parameters

As noted above, because of the higher incidence of neutropenia noted in the major depression study, we examined laboratory data for neutropenia and those findings are discussed further in Section [13.7.3](#). There was also a decrease in white blood cell count over time in the crinecerfont group during the double-blind treatment period compared to placebo. This issue is addressed further in Section [13.7.3](#).

There was no notable difference in mean change or outlier incidence in hemoglobin, hematocrit, or platelets (see [Table 198](#) in Section [23.2.2](#)).

With respect to coagulation parameters, mean PT and partial thromboplastin time (PTT) increased slightly over time in both treatment groups, but the effect was larger in the crinecerfont group (see [Figure 17](#)). INR remained stable in both groups ([Figure 17](#)). There was no notable difference in incidence of outliers in coagulation parameters of INR or PTT between crinecerfont and placebo groups ([Table 46](#)). For study subjects with adverse events classified under the narrow FDA medical query (FMQ) of hemorrhage ([Table 47](#)), all had coagulation study parameters within normal limits, that includes PT, PTT, and INR.

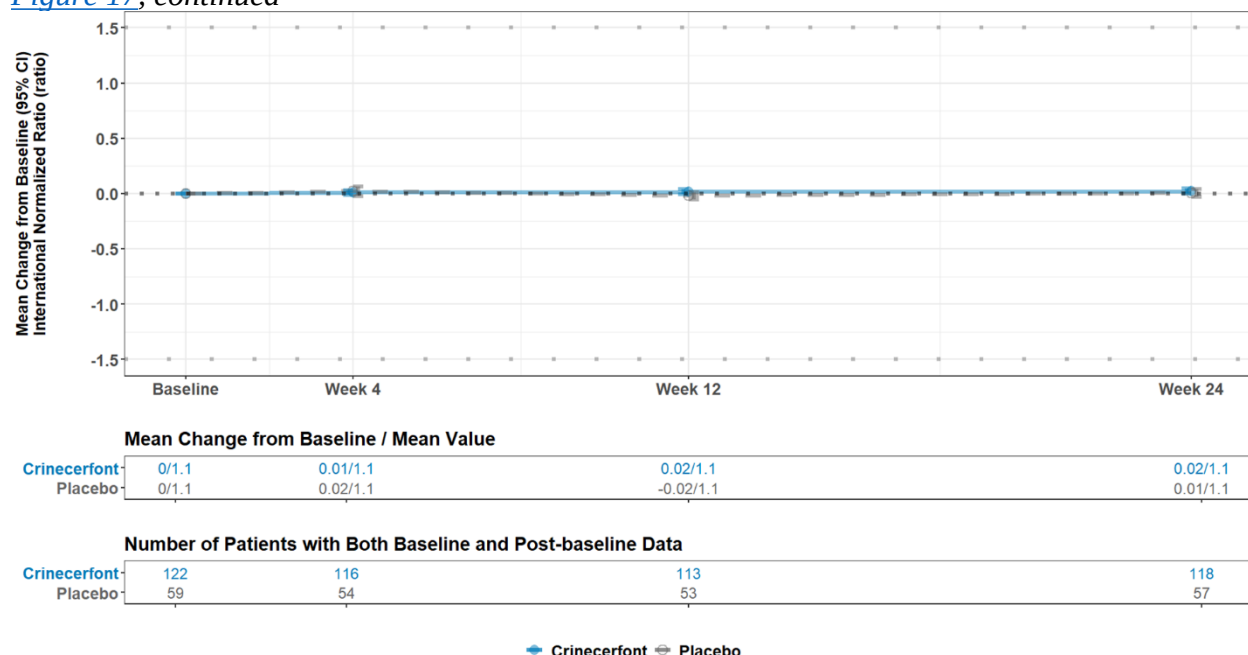
Figure 17. Mean Coagulation Parameter Change From Baseline Over Time, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



Continued

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

Figure 17, continued



Source: adlb.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.

Only central laboratory data are included in the analysis.

Abbreviations: CI, confidence interval

Table 46. Incidence of Coagulation Parameters Transitioning From Normal at Baseline to Above the Normal Range, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Coagulation Studies	Crinecerfont N=122 n/N _w (%)	Placebo N=59 n/N _w (%)
INR, high (sec)		
Level 1 (>1.1× ULN)	3/121 (2.5)	4/59 (6.8)
Level 2 (>1.3× ULN)	1/121 (<1)	2/59 (3.4)
Level 3 (>1.5× ULN)	1/121 (<1)	1/59 (1.7)
PTT, high (sec)		
Level 1 (>1× ULN)	6/121 (6.6)	3/59 (6.8)
Level 2 (>1.21× ULN)	0/121 (0.8)	0/59 (0)
Level 3 (>1.41× ULN)	0/121 (0)	0/59 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; dec., decrease; inc., increase; INR, international normalized ratio; N, number of subjects in treatment arm; n, number of subjects meeting criteria; NA, not applicable; N_w, number of subjects with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cell

Table 47. Adverse Events Within the Hemorrhage FDA Medical Query (Narrow) by Preferred Term, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

FMQ (Narrow) Preferred Term	Crinecerfont N=122 n (%)	Placebo N=59 n (%)	Risk Difference % (95% CI)
Hemorrhage (FMQ)	7 (5.7)	3 (5.1)	0.7 (-8.7, 7.4)
Contusion	2 (1.6)	0	1.6 (-4.5, 5.8)
Eye haematoma	1 (0.8)	0	0.8 (-5.3, 4.5)
Haematemesis	1 (0.8)	0	0.8 (-5.3, 4.5)
Haematochezia	1 (0.8)	0	0.8 (-5.3, 4.5)
Intermenstrual bleeding	1 (0.8)	0	0.8 (-5.3, 4.5)
Ecchymosis	1 (0.8)	1 (1.7)	-0.9 (-8.3, 3.0)
Epistaxis	0	1 (1.7)	-1.7 (-9.0, 1.4)
Haematuria	0	1 (1.7)	-1.7 (-9.0, 1.4)
Vessel puncture site haematoma	0	1 (1.7)	-1.7 (-9.0, 1.4)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term

13.6.2.6.2. Open-Label Treatment Period and Open-Label Extension

Laboratory parameters that were abnormal in the double-blind treatment period were the focus of the assessment of laboratory data from the open-label treatment period and, as needed, the open-label extension data that were submitted in the 120-Day Safety Update.

The incidence of elevated CPK levels in the open-label period decreased compared to the double-blind period, which suggests the effect was not due to study drug. As shown in [Table 48](#), creatine phosphokinase values $>3 \times$ ULN (Level 1 abnormality) decreased in frequency from 11.9% in the placebo double-blind group to none in the placebo/crinecerfont group. The frequency of elevated CPK values at all levels decreased from the crinecerfont DB group to the crinecerfont/crinecerfont group. See [Table 48](#).

Table 48. Subjects With Elevated Creatine Phosphokinase Values Meeting Specified Levels, Safety Population, Trial NBI-74788-CAH3003, Open-Label and Double-Blind Treatment Periods

Laboratory Parameter	Crinecerfont (DB) to Crinecerfont (OL) Weeks 24 to 48 N=117 n/N _w (%)	Crinecerfont (DB) Period Weeks 0 to 24 N=122 n/N _w (%)	Placebo (DB) to Crinecerfont (OL) Weeks 24 to 48 N=57 n/N _w (%)	Placebo (DB) Period Weeks 0 to 24 N=59 n/N _w (%)
CPK, high (U/L)				
Level 1 (>3× ULN)	5/117 (4.3)	11/121 (9.1)	0/57 (0)	7/59 (11.9)
Level 2 (>5× ULN)	4/117 (3.4)	8/121 (6.6)	0/57 (0)	0/59 (0)
Level 3 (>10× ULN)	1/117 (0.9)	5/121 (4.1)	0/57 (0)	0/59 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 24 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Abbreviations: CPK, creatine phosphokinase; DB, double-blind; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OL, open-label; ULN, upper limit of normal

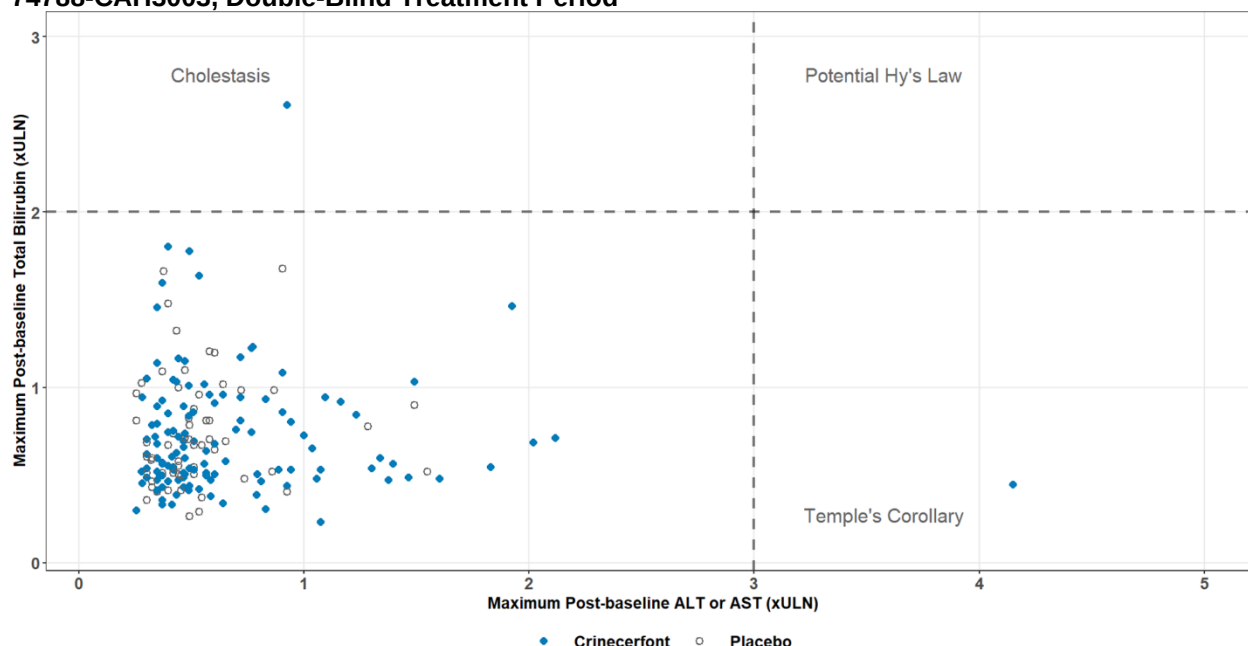
White blood cell and neutrophil count data are discussed further in Section [13.7.3](#).

13.6.2.7. Assessment of Drug-Induced Liver Injury, Trial CAH3003

In rat and dog studies, increased liver weight and hepatocellular hypertrophy were observed, likely due to crinecerfont's induction of drug-metabolizing enzymes. Laboratory data were screened for evidence of drug-induced liver injury to determine cases meeting Hy's Law criteria, defined as any postbaseline total bilirubin equal to or exceeding two times the upper limit of normal (2× ULN) after a postbaseline alanine aminotransferase (ALT) or aspartate aminotransferase (AST) equal to or exceeding 3× ULN. There were no potential cases of Hy's Law during the double-blind ([Figure 18](#)) or open-label treatment periods.

As shown in [Table 49](#), the incidence of excursions in liver parameters outside the normal range during treatment were similar between the crinecerfont and placebo groups. A single subject receiving crinecerfont experienced increase in total bilirubin to >2× ULN without associated transaminase elevation.

Figure 18. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



Source: adlb.xpt; Software: R

Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN after a postbaseline ALT or AST equal to or exceeding 3× ULN. Those subjects who meet total bilirubin equal to or exceeding 2× ULN criteria within 30 days of the ALT or AST equal to or exceeding 3× ULN criteria are circled in red.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

All subjects with at least one postbaseline ALT or AST, bilirubin, and ULN are plotted.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot ..." and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening"

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Table 49. Proportion of Subjects With Elevations in Liver Function Tests, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=122 n/N _w (%)	Placebo N=59 n/N _w (%)	Risk Difference % (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5× ULN)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 2 (>2× ULN)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 3 (>3× ULN)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Alanine aminotransferase, high (U/L)			
Level 1 (>3× ULN)	1/121 (0.8)	0/59 (0)	0.8 (-5.3, 4.6)
Level 2 (>5× ULN)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 3 (>10× ULN)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3× ULN)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 2 (>5× ULN)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 3 (>10× ULN)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)

Laboratory Parameter	Crinecerfont N=122 n/N _w (%)	Placebo N=59 n/N _w (%)	Risk Difference % (95% CI)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5× ULN)	5/121 (4.1)	2/59 (3.4)	0.7 (-7.8, 6.6)
Level 2 (>2× ULN)	1/121 (0.8)	0/59 (0)	0.8 (-5.3, 4.6)
Level 3 (>3× ULN)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

For specific evaluation of drug-induced liver injury (DILI), see the figures "Hepatocellular Drug-Induced Liver Injury Screening Plot..." and "Cholestatic Drug-Induced Liver Injury Screening Plot..." and the tables "Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot..." and "Patients in Each Quadrant for Cholestatic DILI Screening Plot..."

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

13.6.2.8. Vital-Sign Analyses, Trial CAH3003

Review of the vital-sign data did not reveal any safety concerns. There were no clinically significant changes from baseline over time in mean systolic blood pressure, diastolic blood pressure, orthostatic blood pressure, heart rate, respiratory rate, or body temperature in the crinecerfont versus placebo group during the 24-week double-blind treatment period. See Section 23 for additional details ([Figure 78](#), [Figure 79](#), [Figure 80](#), [Figure 81](#), [Figure 82](#), and [Table 199](#)).

13.6.2.9. Subgroup Analyses, Trial CAH3003

There were no significant differences in adverse event rates by demographic subgroups, although some subgroups were small, limiting conclusions ([Table 50](#)).

Table 50. Overview of Treatment-Emergent Adverse Event Rates by Demographic Subgroup, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Characteristic	Crinecerfont N=122 n/N _s (%)	Placebo N=59 n/N _s (%)	Risk Difference % (95% CI)
Sex			
Female	53/61 (86.9)	25/29 (86.2)	0.7 (-13.3, 18.9)
Male	48/61 (78.7)	23/30 (76.7)	2.0 (-14.9, 21.9)
Age group, years			
18 to 25	31/40 (77.5)	20/27 (74.1)	3.4 (-16.9, 25.5)
26 to 35	35/43 (81.4)	18/21 (85.7)	-4.3 (-22.0, 18.3)
36 to 45	20/24 (83.3)	3/4 (75.0)	8.3 (-21.7, 56.4)
46 to 55	15/15 (100)	5/5 (100)	0.0 (-21.2, 44.7)
56 to 65	0/0 (NA)	2/2 (100)	NA
Race			
American Indian or Alaska Native	1/1 (100)	0/0 (NA)	NA
Asian	4/5 (80.0)	0/0 (NA)	NA
Black or African American	2/2 (100)	0/0 (NA)	NA
White	87/107 (81.3)	45/56 (80.4)	1.0 (-11.1, 14.8)
Multiple	1/1 (100)	1/1 (100)	0.0 (-88.5, 88.5)
Other	2/2 (100)	1/1 (100)	0.0 (-74.2, 85.2)
Missing	4/4 (100)	1/1 (100)	0.0 (-54.6, 82.8)

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

Characteristic	Crinecerfont N=122 n/N_s (%)	Placebo N=59 n/N_s (%)	Risk Difference % (95% CI)
Ethnicity			
Hispanic or Latino	4/6 (66.7)	7/8 (87.5)	-20.8 (-62.9, 24.9)
Not Hispanic or Latino	97/116 (83.6)	41/51 (80.4)	3.2 (-8.5, 17.4)
Is in United States			
United States	42/48 (87.5)	18/21 (85.7)	1.8 (-14.1, 23.7)
Non-United States	59/74 (79.7)	30/38 (78.9)	0.8 (-14.1, 18.1)
Baseline BMI			
<30 kg/m ²	52/64 (81.2)	26/32 (81.2)	-0.0 (-15.4, 18.6)
≥30 kg/m ²	49/58 (84.5)	22/27 (81.5)	3.0 (-12.8, 22.9)
Baseline dexamethasone use			
Dexamethasone use	12/17 (70.6)	5/6 (83.3)	-12.7 (-43.3, 32.6)
No dexamethasone use	89/105 (84.8)	43/53 (81.1)	3.6 (-8.1, 17.5)
Baseline glucocorticoid type			
Hydrocortisone alone	57/71 (80.3)	27/34 (79.4)	0.9 (-14.3, 19.1)
Synthetic glucocorticoids	44/51 (86.3)	21/25 (84.0)	2.3 (-13.6, 22.6)
Baseline glucocorticoid dose			
<20 mg/m ² /day	78/97 (80.4)	36/45 (80.0)	0.4 (-12.7, 15.9)
≥20 mg/m ² /day	23/25 (92.0)	12/14 (85.7)	6.3 (-14.3, 33.6)

Source: adae.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

Abbreviations: BMI, body mass index; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm

13.6.2.10. Exposure-Adjusted Analyses, Trial CAH3003

[Table 51](#) shows exposure-adjusted incidence rates in the combined double-blind and open-label treatment periods with a higher rate (per 100 subject-years) in subjects who received crinecerfont. The overall event rate was greater in the placebo group. Coronavirus infection, gastroenteritis, and skin striae are not likely study-drug-related based on mechanism of action.

Table 51. Exposure-Adjusted Adverse Event Incidence Rates Greater in Subjects Who Received Crinecerfont, Trial NBI-74788-CAH3003, Double-Blind and Open-Label Periods Combined

Preferred Term	Crinecerfont (Rate per 100 Subject-Years)	Placebo (Rate per 100 Subject-Years)
Overall	365	442
Fatigue	36	32
Coronavirus infection	21	17
Dizziness	13	6.5
Gastroenteritis	13	3
Arthralgia	10	0
Back pain	10	6
Myalgia	6	0
Decreased appetite	6	3
Insomnia	6	3
Skin striae	9	0

Source: Adapted from Clinical Study Report NBI-74788-CAH3003, Table 37, p115-116.

13.6.3. Safety Results, Trial CAH2006

13.6.3.1. Overview of Treatment-Emergent Adverse Events Summary, Trial CAH2006

13.6.3.1.1. Double-Blind Treatment Period

During the 28-week double-blind placebo-controlled period of Trial CAH2006, the overall rates of adverse events were similar in the crinecerfont (84%) and placebo (82%) groups. One subject in the crinecerfont group (1.4%) compared to four subjects in the placebo group (12%) experienced serious adverse events. Adverse events leading to interruption of study drug occurred more frequently in the placebo group (15%) compared to the crinecerfont group (3%) ([Table 52](#)).

Table 52. Overview of Adverse Events, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Event Category	Crinecerfont N=69 n (%)	Placebo N=33 n (%)	Risk Difference % (95% CI)
Any AE	58 (84.1)	27 (81.8)	2.2 (-12.2, 20.1)
SAE	1 (1.4)	4 (12.1)	-10.7 (-26.1, -1.7)*
AE leading to permanent discontinuation of study drug	2 (2.9)	0	2.9 (-7.7, 10.0)
AE leading to interruption of study drug	2 (2.9)	5 (15.2)	-12.3 (-28.4, -1.7)*

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Severity as assessed by the investigator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with at least one event; SAE, serious adverse event

13.6.3.1.2. Open-Label Treatment Period (Weeks 28 to 52)

The overall rate of any adverse event decreased from 82% in the placebo DB period to 74% during the open-label period in the placebo/crinecerfont group and decreased from 84% in the crinecerfont DB period to 70% during the open-label period in the crinecerfont/crinecerfont group ([Table 53](#)), which suggests improved tolerability of crinecerfont for the subjects who remained in the trial and continued treatment with crinecerfont. The rate of serious adverse events decreased from 12% in the placebo DB period to 6.5% during the open-label period in the placebo/crinecerfont group and were similar to the crinecerfont/crinecerfont group (6%). These data do not raise any concerns with longer-term treatment.

Table 53. Overview of Adverse Events, Safety Population, Trial NBI-74788-CAH2006, Open-Label and Double-Blind Treatment Periods

Event Category	Crinecerfont (DB) to Crinecerfont (OL) Weeks 28 to 52 N=66 n (%)	Crinecerfont (DB) Period Weeks 0 to 28 N=69 n (%)	Placebo (DB) to Crinecerfont (OL) Weeks 28 to 52 N=31 n (%)	Placebo (DB) Period Weeks 0 to 28 N=33 n (%)
Any AE	46 (69.7)	58 (84.1)	23 (74.2)	27 (81.8)
SAE	4 (6.1)	1 (1.4)	2 (6.5)	4 (12.1)
AE leading to permanent discontinuation of study drug	0	2 (2.9)	0	0
AE leading to interruption of study drug	1 (1.5)	2 (2.9)	2 (6.5)	5 (15.2)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 28 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Severity as assessed by the investigator.

Abbreviations: AE, adverse event; DB, double-blind; N, number of subjects in treatment arm; n, number of subjects with at least one event; OL, open-label; SAE, serious adverse event

13.6.3.1.3. Open-Label Extension (Week 52 Onward)

All 97 subjects who started the open-label treatment period completed open-label treatment through Week 52. Of the 97 who completed the open-label treatment period, 93 (97%) continued in the open-label extension, which is ongoing.

The adverse event rate decreased to 42% among subjects continuing in the open-label extension, with the majority of events graded as mild or moderate ([Table 54](#)).

Table 54. Summary of Treatment-Emergent Adverse Events, Trial NBI-74788-CAH2006, Open-Label Extension (Week 52 Onward)

TEAE Type	All Subjects (N=93) n (%)
Subjects with:	
Any TEAE	39 (41.9)
Any SAE	3 (3.2)
Any TEAE leading to study drug discontinuation	1 (1.1)
Any TEAE resulting in death	0

Source: Safety Update NBI-74788-CAH2006, Table 14.4.3.1.

Abbreviations: SAE, serious adverse event; TEAE, treatment-emergent adverse event

13.6.3.2. Deaths, Trial CAH2006

There have been no deaths reported in Trial CAH2006.

13.6.3.3. Serious Treatment-Emergent Adverse Events, Trial CAH2006

13.6.3.3.1. Double-Blind Treatment Period

In Trial CAH2006, the overall rate of serious TEAEs was higher in the placebo group (12%, four subjects) compared to the crinecerfont group (1.4%, one subject) during the 28-week double-blind treatment period ([Table 55](#)).

The one serious TEAE of pyrexia occurring in the crinecerfont group during the double-blind treatment period was more likely related to an infectious etiology, given the subject's improvement with treatment in the emergency department and in the setting of continued crinecerfont treatment:

- Pyrexia occurred in a 12-year-old-male who presented to the emergency department with a temperature of 38.2°C, vomiting, and headache on Study Day 61. Attempts at oral stress-dose hydrocortisone at home were unsuccessful due to vomiting. In the emergency department, he was treated with intravenous hydration, fluids, dextrose, and hydrocortisone. His condition improved and he was discharged the same day. No changes were made to his study drug regimen.

Table 55. Subjects With Serious Adverse Events by Preferred Term, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Preferred Term	Crinecerfont N=69 n (%)	Placebo N=33 n (%)	Risk Difference % (95% CI)
Any SAE	1 (1.4)	4 (12.1)	-10.7 (-26.1, -1.7)*
Vomiting	0	2 (6.1)	-6.1 (-19.7, -0.5)*
Pyrexia	1 (1.4)	0	1.4 (-9.1, 7.8)
Chest pain	0	1 (3.0)	-3.0 (-15.4, 2.4)
Gastroenteritis	0	1 (3.0)	-3.0 (-15.4, 2.4)
Gastroenteritis norovirus	0	1 (3.0)	-3.0 (-15.4, 2.4)
Gastroenteritis viral	0	1 (3.0)	-3.0 (-15.4, 2.4)
Infectious mononucleosis	0	1 (3.0)	-3.0 (-15.4, 2.4)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Serious adverse events defined as any untoward medical occurrence that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Infectious mononucleosis replaces: Pharyngitis

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; SAE, serious adverse event

13.6.3.3.2. SAEs During Open-Label Treatment Period (Weeks 28 to 52)

[Table 56](#) lists the serious TEAEs that began during the open-label treatment period, according to treatment received in the double-blind phase (i.e., placebo or crinecerfont). There were six events in six subjects.

Narratives for the events (preferred terms) of vomiting and gastritis were reviewed and are considered unrelated to study drug, due either to identification of an alternate cause or an unlikely relationship to pharmacology of crinecerfont.

Details of the three remaining SAEs, none of which are likely study-drug-related, follow:

- An SAE of hypotension occurred in a 6-year-old female on amlodipine. Her hypotension resolved when her amlodipine dose was reduced. This event can be attributed to effect of antihypertensive medication.
- A seizure occurred in a 5-year-old female on Study Day 222 that led to hospitalization and study drug interruption for 1 day. Initial laboratory evaluation and brain imaging was normal. Further evaluation included chromosomal microarray testing that was suspicious for 15q duplication syndrome, which may be associated with epilepsy. This case represents initial presentation of epilepsy secondary to a chromosomal abnormality.
- An SAE of acute adrenocortical insufficiency occurred in a 7-year-old female on Study Day 223 that led to interruption of study drug for 2 days. She was admitted to the hospital after presenting with vomiting and diarrhea. She vomited her stress-dose hydrocortisone. Evaluation was consistent with adrenal crisis (hypoglycemia, hyponatremia, metabolic acidosis). A viral gastroenteritis panel was positive for norovirus. She was treated with intravenous fluids, dextrose, stress-dose hydrocortisone, fludrocortisone, and ondansetron. Her condition significantly improved after two days. In this case, acute adrenal insufficiency was considered secondary to norovirus gastroenteritis.

Table 56. Subjects With Serious Adverse Events by Preferred Term, Safety Population, Trial NBI-74788-CAH2006, Open-Label Treatment Period

Preferred Term	Crinecerfont (DB) to Crinecerfont (OL) Weeks 28 to 52 N=66 n (%)	Placebo (DB) to Crinecerfont (OL) Weeks 28 to 52 N=31 n (%)
Any SAE	4 (6.1)	2 (6.5)
Adrenocortical insufficiency acute	1 (1.5)	0
Vomiting	1 (1.5)	0
Gastritis	0	1 (3.2)
Influenza	1 (1.5)	0
Seizure	0	1 (3.2)
Hypotension	1 (1.5)	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 28 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Abbreviations: AE, adverse event; DB, double-blind; N, number of subjects in treatment arm; n, number of subjects with adverse event; OL, open-label; SAE, serious adverse event

13.6.3.3.3. Serious Adverse Events Reported in the Open-Label Extension (Week 52 Onward)

Three subjects experienced serious adverse events in the open-label extension that were newly reported in the 120-day safety update. Narratives for the events (preferred terms) of blood CPK increased, Norovirus infection, and cerebrospinal fluid leakage were reviewed, and these events are considered unrelated to study drug due either to identification of an alternate cause, or unlikely relationship to the pharmacology of crinecerfont. The event of blood CPK increased was temporally related to isotretinoin. The event of cerebrospinal fluid leakage was related to cranio-spinal surgery for Chiari malformation.

13.6.3.4. Adverse Events Leading to Treatment Discontinuation, Trial CAH2006

13.6.3.4.1. Double-Blind Treatment Period

Two subjects (3%) in the crinecerfont group and none in the placebo group experienced an adverse event leading to study drug discontinuation during the 28-week double-blind treatment period ([Table 57](#)).

The symptoms occurring in the two subjects leading to study drug discontinuation (abdominal pain, nausea, motion sickness, retching, myalgias, dizziness) are described below:

- Abdominal pain, nausea, and myalgias occurred in a 15-year-old female on Study Day 126. Study drug was withdrawn on Study Day 196 because of continued symptoms. Symptoms were resolved on Study Day 224, off study drug.
- Dizziness, nausea, motion sickness, and retching occurred in a 15-year-old female leading to study drug discontinuation on Study Day 191. She also experienced anxiety, depression, and suicidal ideation. Dizziness occurred within a few days of study drug initiation. Nausea occurred on Study Day 58. Motion sickness occurred on Study Day 149. Anxiety, depression, and suicidal ideation occurred after about 5 months on study drug. Retching occurred after about 6 months on study drug. Dizziness and retching were resolved about 5 months after study drug was discontinued.

Table 57. Subjects With Adverse Events Leading to Treatment Discontinuation by Preferred Term, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Preferred Term	Crinecerfont	Placebo	Risk Difference % (95% CI)
	N=69 n (%)	N=33 n (%)	
Any AE leading to discontinuation	2 (2.9)	0	2.9 (-7.7, 10.0)
Motion sickness ^a	1 (1.4)	0	1.4 (-9.1, 7.8)
Nausea ^{a,b}	2 (2.9)	0	2.9 (-7.7, 10.0)
Abdominal pain ^b	1 (1.4)	0	1.4 (-9.1, 7.8)
Retching ^a	1 (1.4)	0	1.4 (-9.1, 7.8)
Myalgia ^b	1 (1.4)	0	1.4 (-9.1, 7.8)
Dizziness ^a	1 (1.4)	0	1.4 (-9.1, 7.8)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abdominal pain replaces: Abdominal pain upper

Myalgia replaces: Pain

^a Motion sickness, nausea, retching, and dizziness occurred in the same subject

^b Nausea, abdominal pain, and myalgia occurred in the same subject

Abbreviations: AE, adverse event; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event

13.6.3.4.2. Open-Label Treatment Period

No additional subjects experienced an adverse event leading to study drug discontinuation during the open-label treatment period.

13.6.3.4.3. Open-Label Extension (Week 52 Onward)

One subject, a 14-year-old male, discontinued study drug during the open-label extension for a suicide attempt (preferred term) as specified per protocol. After the data cutoff, the investigations indicated that the event term should be corrected to “suicidal ideation” because the subject did not have a plan and did not make a suicide attempt. He had a history of anxiety, depression, and attention deficit hyperactivity disorder. Concomitant medications included bupropion, fluoxetine, hydroxyzine, aripiprazole, and isotretinoin. The subject visited his family home construction site and had a thought that if he fell off the roof, he would die.

13.6.3.5. Treatment-Emergent Adverse Events, Trial CAH2006

13.6.3.5.1. Double-Blind Treatment Period

[Table 58](#) lists the adverse events occurring at $\geq 2\%$ frequency in the 28-week double-blind treatment period and at a greater frequency in the crinecerfont group than in the placebo group. Headache and upper respiratory infection had the largest between-group differences. Upper respiratory tract infection is not likely study-drug-related based on the mechanism of action of the drug. Similarly, the adverse events of influenza, nasal congestion, pharyngitis streptococcal, viral infection, ear infection, pharyngitis, rhinorrhea, oropharyngeal pain, and seasonal allergy are not likely study-drug-related.

Table 58. Common Adverse Events, Occurring at $\geq 2\%$ Frequency and With Greater Frequency in the Crinecerfont vs. Placebo Group, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Preferred Term	Crinecerfont N=69 n (%)	Placebo N=33 n (%)	Risk Difference % (95% CI)
Any AE	58 (84.1)	27 (81.8)	2.2 (-12.2, 20.1)
Headache	17 (24.6)	2 (6.1)	18.6 (2.9, 31.4)*
Upper resp tract infection	8 (11.6)	0	11.6 (0.7, 21.3)*
Abdominal pain	5 (7)	0	8.7 (-2.1, 17.8)
Influenza	6 (8.7)	2 (6.1)	2.6 (-11.8, 13.0)
Fatigue	5 (7.2)	0	7.2 (-3.5, 15.9)
Nasal congestion	5 (7.2)	1 (3.0)	4.2 (-8.7, 13.5)
Pharyngitis streptococcal	4 (5.8)	0	5.8 (-4.9, 14.0)
Viral infection	4 (5.8)	1 (3.0)	2.8 (-10.1, 11.6)
Ear infection	3 (4.3)	0	4.3 (-6.3, 12.1)
Epistaxis	3 (4.3)	0	4.3 (-6.3, 12.1)
Pharyngitis	3 (4.3)	0	4.3 (-6.3, 12.1)
Rhinorrhoea	3 (4.3)	0	4.3 (-6.3, 12.1)
Oropharyngeal pain	3 (4.3)	1 (3.0)	1.3 (-11.4, 9.6)
Abdominal pain upper	2 (2.9)	0	2.9 (-7.7, 10.0)
Anxiety	2 (2.9)	0	2.9 (-7.7, 10.0)
Attention deficit hyperactivity disorder	2 (2.9)	0	2.9 (-7.7, 10.0)
Contusion	2 (2.9)	0	2.9 (-7.7, 10.0)

Preferred Term	Crinecerfont N=69 n (%)	Placebo N=33 n (%)	Risk Difference % (95% CI)
Hypersensitivity	2 (2.9)	0	2.9 (-7.7, 10.0)
Seasonal allergy	2 (2.9)	0	2.9 (-7.7, 10.0)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 28 weeks.

Coded as MedDRA preferred terms.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Abdominal pain replaces: Abdominal pain upper

Abbreviations: AE, adverse event; CI, confidence interval; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

13.6.3.5.2. Open-Label Treatment Period (Weeks 28 to 52)

During the open-label treatment period, the rate of any AE decreased from 84% in the crinecerfont DB group to 70% in the crinecerfont/crinecerfont group and decreased from 82% in the placebo DB group to 74% in the placebo/crinecerfont group ([Table 59](#)).

Adverse event preferred terms that increased in frequency in subjects transitioning from placebo to crinecerfont were considered possibly related to study drug with the caveat that the small sample size significantly limits interpretation. As shown in [Table 59](#) in the column labeled “Placebo (DB) to Crinecerfont (OL) Week 28 to Week 52,” only headache and abdominal pain met those criteria. It is possible that these events relate to symptoms of glucocorticoid withdrawal rather than crinecerfont itself. Both headache and abdominal pain also decreased in frequency from the crinecerfont DB group to the crinecerfont/crinecerfont group, suggesting development of tolerance to reduction in glucocorticoid dose or to crinecerfont treatment.

Table 59. Adverse Events in the Open-Label (OL) Treatment Period, Occurring at ≥4% Frequency, Safety Population, Trial NBI-74788-CAH2006, Double-Blind or OL Treatment Periods

Preferred Term	Crinecerfont (DB) to Crinecerfont (OL) Weeks 28 to 52 N=66 n (%)	Crinecerfont (DB) Period Weeks 0 to 28 N=69 n (%)	Placebo (DB) to Crinecerfont (OL) Weeks 28 to 52 N=31 n (%)	Placebo (DB) Period Weeks 0 to 28 N=33 n (%)
Any AE	46 (69.7)	58 (84.1)	23 (74.2)	27 (81.8)
Pyrexia	15 (22.7)	16 (23.2)	5 (16.1)	8 (24.2)
Headache	9 (13.6)	17 (24.6)	7 (22.6)	2 (6.1)
Vomiting	6 (9.1)	10 (14.5)	7 (22.6)	10 (30.3)
Influenza	5 (7.6)	6 (8.7)	2 (6.5)	2 (6.1)
Nasopharyngitis	5 (7.6)	7 (10.1)	1 (3.2)	6 (18.2)
Upper respiratory tract infection	4 (6.1)	8 (11.6)	1 (3.2)	0
Fatigue	5 (7.6)	5 (7.2)	1 (3.2)	0
Abdominal pain	4 (6.1)	6 (8.7)	2 (6.5)	0
Nausea	4 (6.1)	4 (5.8)	0	2 (6.1)
Nasal congestion	2 (3.0)	5 (7.2)	1 (3.2)	1 (3.0)
Oropharyngeal pain	5 (7.6)	3 (4.3)	0	1 (3.0)

Preferred Term	Crinecerfont (DB) to Crinecerfont (OL) Weeks 28 to 52 N=66 n (%)	Crinecerfont (DB) Period Weeks 0 to 28 N=69 n (%)	Placebo (DB) to Crinecerfont (OL) Weeks 28 to 52 N=31 n (%)	Placebo (DB) Period Weeks 0 to 28 N=33 n (%)
Pharyngitis streptococcal	1 (1.5)	4 (5.8)	0	0
Viral infection	1 (1.5)	4 (5.8)	0	1 (3.0)
Rhinorrhoea	1 (1.5)	3 (4.3)	0	0
Ear infection	2 (3.0)	3 (4.3)	0	0
Epistaxis	0	3 (4.3)	0	0
Pharyngitis	1 (1.5)	3 (4.3)	1 (3.2)	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 28 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Coded as MedDRA preferred terms.

Abdominal pain replaces: Abdominal pain upper

Abbreviations: AE, adverse event; DB, double-blind; MedDRA, Medical Dictionary for Regulatory Activities; N, number of subjects in treatment arm; n, number of subjects with adverse event

13.6.3.6. Laboratory Findings, Trial CAH2006

See the schedule of assessments in Section [21](#) for the frequency of laboratory monitoring.

Laboratory data for CPK, neutrophil count, and coagulation parameters were examined more closely for the following reasons:

- Elevated CPK levels were noted in the adult study.
- A higher incidence of neutropenia was noted in a phase 2 study of crinecerfont in subjects with major depressive disorder (see Section [13.2](#)).
- Nonclinical studies of crinecerfont tosylate formulation were associated with coagulopathy (prolongation of PT and APTT and/or bleeding) and mortality in repeat-dose rat studies. Subsequently, the tosylate salt formulation was replaced with a free-base form, which was used for the clinical studies. In chronic rat studies with crinecerfont free base, no mortality or bleeding effects were noted; however, changes in coagulation parameters (prolongation of PT up to 60%, and APTT up to 90%) were observed at 1250 mg/kg/day (6-fold MRHD exposure). Similar findings (prolongation of PT) were observed in the chronic dog study conducted with crinecerfont free base but without any other coagulopathy up to 1000 mg/kg/day (5-fold MRHD exposure).
- Neutropenia and white blood cell count findings are discussed in detail in Section [13.7.3](#).

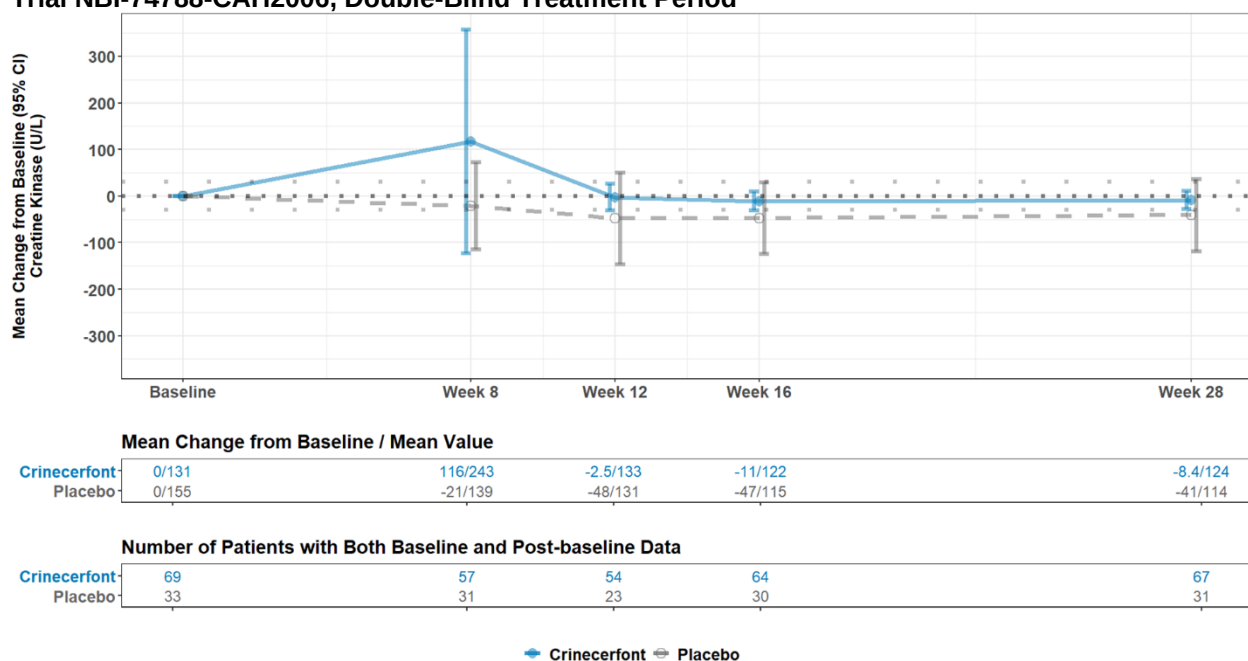
13.6.3.6.1. Double-Blind Treatment Period

13.6.3.6.1.1. Chemistry Parameters

The mean change in CPK levels from baseline over time was similar in both the crinecerfont and placebo groups, with a peak at Week 8 in the crinecerfont group ([Figure 19](#)). Elevated CPK values occurred in one subject in both the crinecerfont (1.4%) and placebo (3%) groups during the 28-week double-blind treatment period, without significant difference between the two groups ([Table 200](#)).

According to the Applicant, the instances of increased CPK levels were associated with significant physical exertion and an increased isotretinoin dose in one case. The levels improved with cessation of the inciting factor. No cases of increased CPK resulted in study treatment discontinuation. There were no reported cases of rhabdomyolysis. The elevated CPK levels are not likely drug-related because elevated levels were explained by other factors and there is no mechanistic evidence of causality.

Figure 19. Mean Creatinine Phosphokinase Change From Baseline Over Time, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period



Source: adlb.xpt; Software: R
Abbreviations: CI, confidence interval

Table 60. Subjects With CPK Values Above the Normal Limit, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=69 n/N _w (%)	Placebo N=33 n/N _w (%)	Risk Difference % (95% CI)
CPK, high (U/L)			
Level 1 (>3× ULN)	1/69 (1.4)	1/33 (3.0)	-1.6 (-14.1, 5.2)
Level 2 (>5× ULN)	1/69 (1.4)	0/33 (0)	1.4 (-9.1, 7.8)
Level 3 (>10× ULN)	1/69 (1.4)	0/33 (0)	1.4 (-9.1, 7.8)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

There were no clinically important differences with respect to median change in chemistry parameters (i.e., electrolytes, renal and hepatic function) or incidence of excursions outside the normal range during the double-blind treatment period. Refer to Section 23.4 for summary tables of incidence of chemistry outliers during the double-blind treatment period ([Table 200](#) for chemistry values and [Table 201](#) for renal function values).

There was generally a very low prevalence of abnormal laboratory findings suggestive of adrenal insufficiency (low sodium, high potassium, low glucose, high blood urea nitrogen) and incidences were similar between the crinecerfont and placebo groups. The 95% CI of the risk difference crossed zero in all cases ([Table 61](#)).

Table 61. Subjects With Laboratory Excursions Potentially Indicative of Adrenal Insufficiency, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=69 n/N _w (%)	Placebo N=33 n/N _w (%)	Risk Difference % (95% CI)
Sodium, low (mEq/L)			
Level 1 (<132)	1/69 (1.4)	0/33 (0)	1.4 (-9.1, 7.8)
Level 2 (<130)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (<125)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Potassium, high (mEq/L)			
Level 1 (>5.5)	1/69 (1.4)	0/33 (0)	1.4 (-9.1, 7.8)
Level 2 (>6)	1/69 (1.4)	0/33 (0)	1.4 (-9.1, 7.8)
Level 3 (>6.5)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Glucose, low (mg/dL)			
Level 1 (<70)	5/69 (7.2)	2/33 (6.1)	1.2 (-13.1, 11.2)
Level 2 (<54)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (<40)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Blood urea nitrogen, high (mg/dL)			
Level 1 (>23)	1/69 (1.4)	1/33 (3.0)	-1.6 (-14.1, 5.2)
Level 2 (>27)	0/69 (0)	1/33 (3.0)	-3.0 (-15.4, 2.4)
Level 3 (>31)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

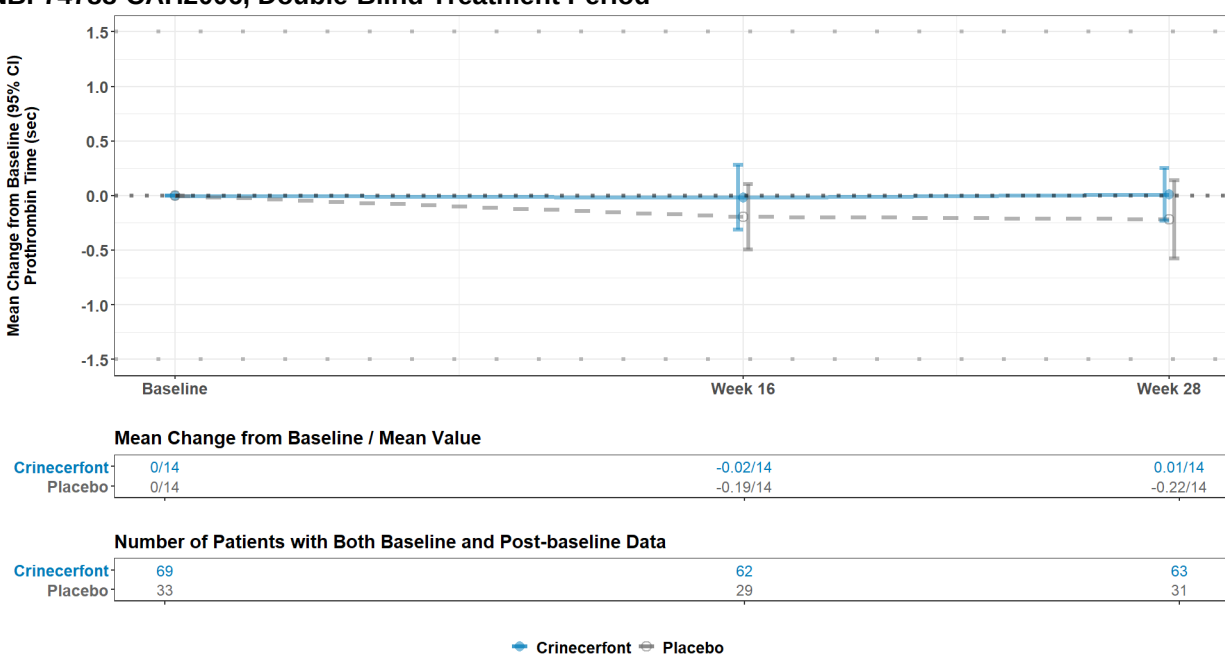
Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

13.6.3.6.1.2. Hematology Parameters

There was no notable difference in mean change or outlier incidence in hemoglobin, hematocrit, or platelets (see [Table 203](#) in Section [23.4](#)).

There was no notable difference in mean change in coagulation parameters ([Figure 20](#)) over the 28-week treatment period. There was a higher incidence of transitions from normal at baseline to above normal during treatment in elevated PTT for the crinecerfont group (7%) compared to the placebo group (3%) ([Table 62](#)). However, all such excursions were Level 1 in severity and are not considered clinically meaningful. None of the five subjects with elevated PTT experienced an adverse event related to hemorrhage.

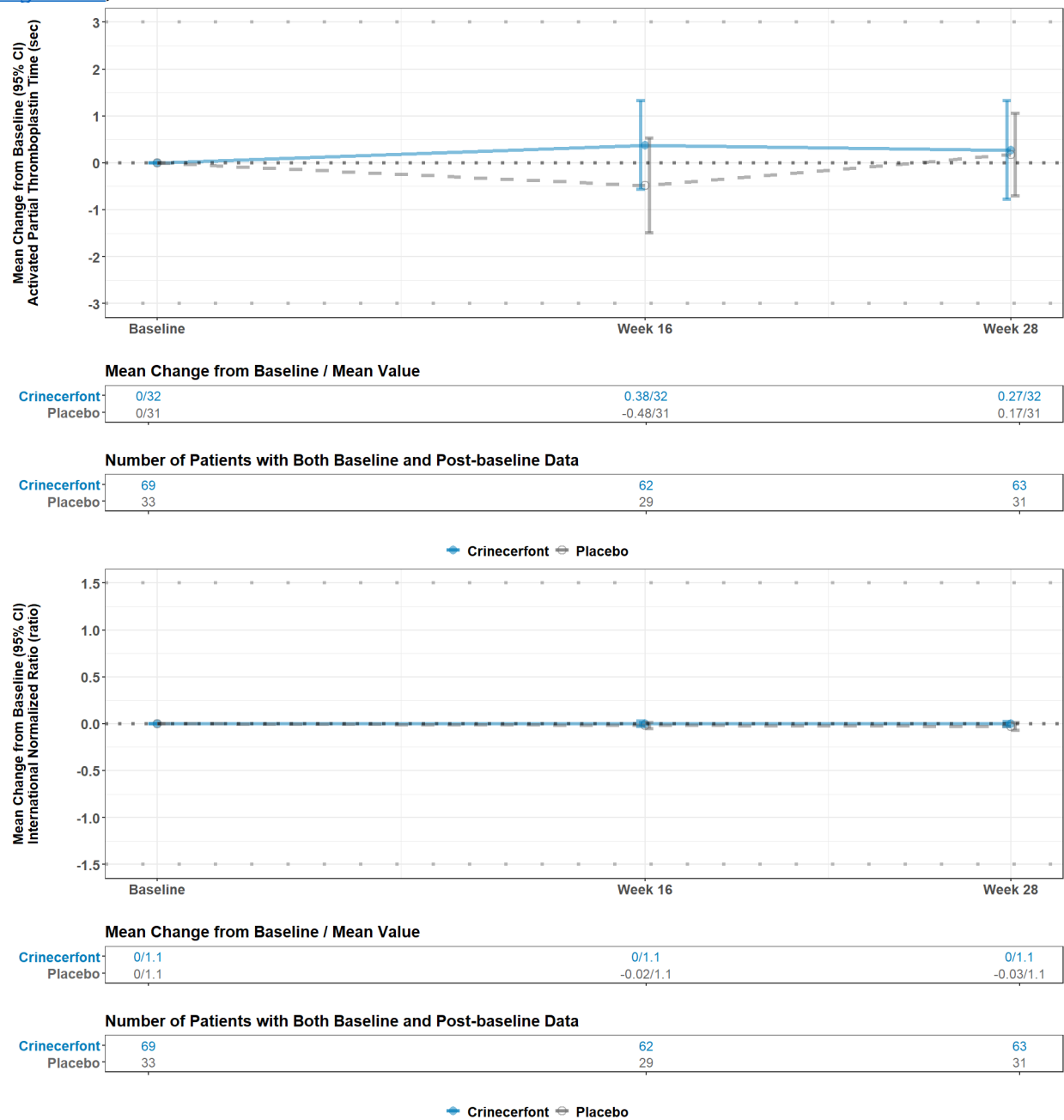
Figure 20. Mean Coagulation Parameter Change From Baseline Over Time, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period



Continued

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

Figure 20, continued



Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.

Table 62. Incidence of Coagulation Parameters Transitioning From Normal at Baseline to Above the Normal Range, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=69 n (%)	Placebo N=33 n (%)
Coagulation studies		
INR		
Level 1 (>1.1× ULN)	1 (<1)	0
Level 2 (>1.3× ULN)	0	0
Level 3 (>1.5× ULN)	0	0
PTT, high (sec)		
Level 1 (>1× ULN)	5 (7)	0
Level 2 (>1.21× ULN)	0	0
Level 3 (>1.41× ULN)	0	0

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 28 weeks.

Abbreviations: INR, international normalized ratio; N, number of subjects in treatment arm; n, number of subjects meeting criteria; PTT, partial thromboplastin time; ULN, upper limit of normal

For study subjects with adverse events classified under the narrow FMQ of hemorrhage ([Table 63](#)), all except one had coagulation study parameters within normal limits, to include PT, PTT, and INR. The one subject whose coagulation study parameters were not completely normal had rectal hemorrhage and a slightly elevated INR of 1.3 at Week 28 (normal range 0.8 to 1.2) compared to a baseline level of 1.1. The PT and PTT were normal. It is unlikely that the rectal hemorrhage was related to mild elevation in INR.

Table 63. Adverse Events Within the Hemorrhage FDA Medical Query (Narrow) by Preferred Term, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

FMQ (Narrow) Preferred Term	Crinecerfont N=69 n (%)	Placebo N=33 n (%)	Risk Difference % (95% CI)
Hemorrhage (FMQ)	6 (8.7)	0	8.7 (-2.1, 17.8)
Epistaxis ^a	3 (4.3)	0	4.3 (-6.3, 12.1)
Contusion ^a	2 (2.9)	0	2.9 (-7.7, 10.0)
Eye contusion	1 (1.4)	0	1.4 (-9.1, 7.8)
Rectal haemorrhage	1 (1.4)	0	1.4 (-9.1, 7.8)

Source: адае.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

See the table "Patients With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)..."

^a Epistaxis and contusion occurred in the same subject

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

13.6.3.6.2. Open-Label Treatment Period

As was done for the adult study (Section [13.6.2.6.2](#)), laboratory parameters that were abnormal in the double-blind treatment period were the focus of the assessment of laboratory data from the open-label treatment period. Reassuringly, the incidence of elevated CPK levels in the open-label period was low and did not increase in the group of subjects who transitioned from placebo to crinecerfont (see [Table 64](#)).

Table 64. Subjects With Elevated Creatine Phosphokinase Values Meeting Specified Levels, Safety Population, Trial NBI-74788-CAH2006, Open-Label and Double-Blind Treatment Periods

Laboratory Parameter	Crinecerfont (DB) to Crinecerfont (OL) Weeks 28 to 52 N=66 n/N _w (%)	Crinecerfont (DB) Period Weeks 0 to 28 N=69 n/N _w (%)	Placebo (DB) to Crinecerfont (OL) Weeks 28 to 52 N=31 n/N _w (%)	Placebo (DB) Period Weeks 0 to 28 N=33 n/N _w (%)
CPK, high (U/L)				
Level 1 (>3× ULN)	1/66 (1.5)	1/69 (1.4)	0/31 (0)	1/33 (3.0)
Level 2 (>5× ULN)	1/66 (1.5)	1/69 (1.4)	0/31 (0)	0/33 (0)
Level 3 (>10× ULN)	0/66 (0)	1/69 (1.4)	0/31 (0)	0/33 (0)

Source: adlb.xpt; Software: R

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 28 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Abbreviations: CPK, creatine phosphokinase; DB, double-blind; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OL, open-label; ULN, upper limit of normal

The incidence of elevated PTT levels was similar in the open-label period and the double-blind period ([Table 65](#)). It is reassuring that the incidence did not increase during this treatment phase and that excursions above normal were small.

Table 65. Incidence of Coagulation Parameters Outside the Normal Range, Safety Population, Trial NBI-74788-CAH2006, Open-Label and Double-Blind Treatment Periods

Laboratory Parameter	Crinecerfont (DB) to Crinecerfont (OL) Weeks 28 to 52 N=66	Crinecerfont (DB) Period Weeks 0 to 28 N=69	Placebo (DB) to Crinecerfont (OL) Weeks 28 to 52 N=31	Placebo (DB) Period Weeks 0 to 28 N=33
	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)
PTT, high (sec)				
Level 1 (>1× ULN)	6/66 (9.1)	7/69 (10.1)	2/31 (6.5)	1/32 (3.1)
Level 2 (>1.21× ULN)	0/66 (0)	1/69 (1.4)	0/31 (0)	0/32 (0)
Level 3 (>1.41× ULN)	0/66 (0)	0/69 (0)	0/31 (0)	0/32 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

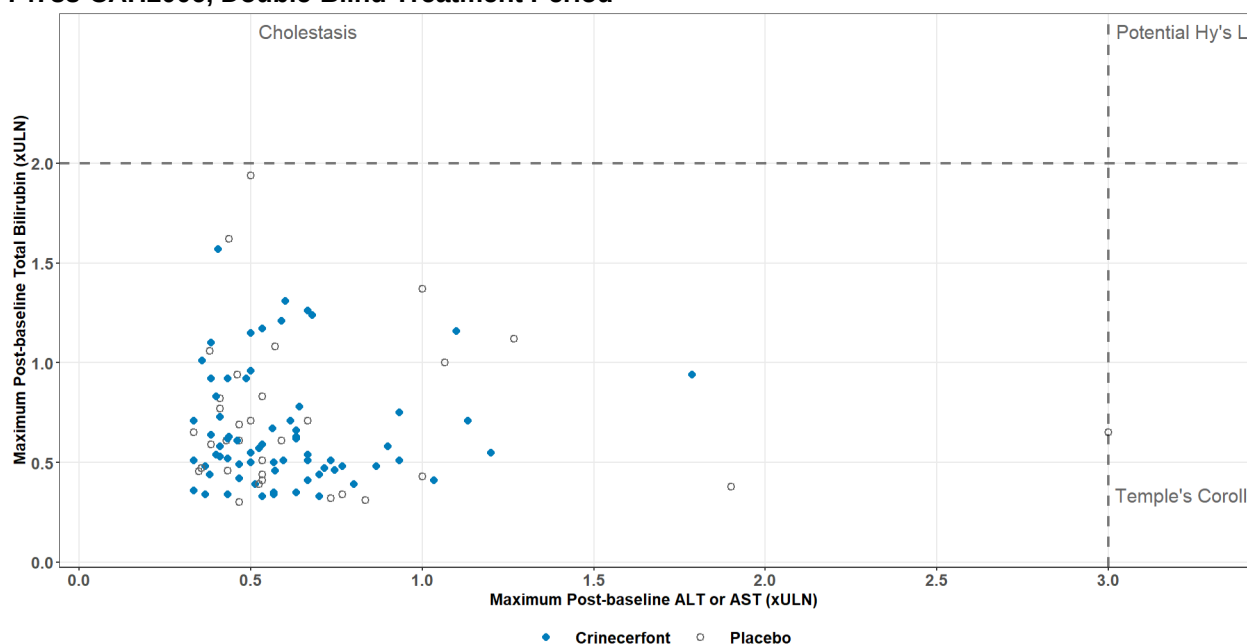
Duration is 28 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Abbreviations: DB, double-blind; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OL, open-label; PTT, partial thromboplastin time; ULN, upper limit of normal

13.6.3.7. Assessment of Drug-Induced Liver Injury, Trial CAH2006

In rat and dog studies, increased liver weight and hepatocellular hypertrophy were observed, likely due to crinecerfont's induction of drug-metabolizing enzymes. Laboratory data were screened for evidence of drug-induced liver injury to determine cases meeting Hy's law criteria, defined as any postbaseline total bilirubin equal to or exceeding 2× ULN after a postbaseline ALT or AST equal to or exceeding 3× ULN. There were no potential cases of Hy's Law during the double-blind (see [Figure 21](#)) or open-label treatment periods. In addition, outlier analysis showed no increased incidence of abnormal liver function tests for the crinecerfont group compared to placebo (see [Figure 21](#)).

Figure 21. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period



Source: adlb.xpt; Software: R

Each data point represents a subject plotted by their maximum ALT or AST versus their maximum total bilirubin values in the postbaseline period.

A potential Hy's Law case was defined as having any postbaseline total bilirubin equal to or exceeding 2× ULN after a postbaseline ALT or AST equal to or exceeding 3× ULN. Those subjects who meet total bilirubin equal to or exceeding 2× ULN criteria within 30 days of the ALT or AST equal to or exceeding 3× ULN criteria are circled in red.

The within 30 days analysis window rule does not apply to cholestasis and temple's corollary cases.

All subjects with at least one postbaseline ALT or AST, bilirubin and ULN are plotted.

For number of subjects in each quadrant, see the table "Subjects in Each Quadrant for Potential Hepatocellular Drug-Induced Liver Injury Screening Plot ..." and the listing "Listing of Subjects in Hepatocellular Drug-Induced Liver Injury Screening...."

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ULN, upper limit of normal

Table 66. Subjects With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=69 n/N _w (%)	Placebo N=33 n/N _w (%)	Risk Difference % (95% CI)
Alkaline phosphatase, high (U/L)			
Level 1 (>1.5× ULN)	2/69 (2.9)	0/33 (0)	2.9 (-7.7, 10.0)
Level 2 (>2× ULN)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (>3× ULN)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Alanine aminotransferase, high (U/L)			
Level 1 (>3× ULN)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 2 (>5× ULN)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (>10× ULN)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Aspartate aminotransferase, high (U/L)			
Level 1 (>3× ULN)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 2 (>5× ULN)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (>10× ULN)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)

Laboratory Parameter	Crinecerfont N=69 n/N _w (%)	Placebo N=33 n/N _w (%)	Risk Difference % (95% CI)
Bilirubin, total, high (mg/dL)			
Level 1 (>1.5× ULN)	1/69 (1.4)	2/33 (6.1)	-4.6 (-18.4, 2.8)
Level 2 (>2× ULN)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (>3× ULN)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

For specific evaluation of drug-induced liver injury (DILI), see the figures "Hepatocellular Drug-Induced Liver Injury Screening Plot..." and "Cholestatic Drug-Induced Liver Injury Screening Plot..." and the tables "Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot..." and "Patients in Each Quadrant for Cholestatic DILI Screening Plot..."

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

13.6.3.8. Vital-Sign Analyses, Trial CAH2006

Review of the vital-sign data did not reveal any safety concerns. There were no significant changes from baseline over time in mean systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, or body temperature in the crinecerfont group versus placebo group during the 28-week double-blind treatment period. See Section [23.5](#) for additional details ([Table 85](#), [Table 86](#), [Table 87](#), [Table 88](#), and [Table 89](#)).

13.6.3.9. Subgroup Analyses, Trial CAH2006

There were no notable differences in adverse event rates by demographic subgroup, stage of pubertal development, or baseline androstenedione level ([Table 67](#)), though conclusions are limited by the small study sample size.

Table 67. Overview of Treatment-Emergent Adverse Event Rates by Demographic Subgroup, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Characteristic	Crinecerfont N=69 n/N _s (%)	Placebo N=33 n/N _s (%)	Risk Difference % (95% CI)
Sex			
Female	28/34 (82.4)	12/15 (80.0)	2.4 (-19.1, 30.1)
Male	30/35 (85.7)	15/18 (83.3)	2.4 (-17.0, 27.1)
Age group, years			
2 to <12	26/31 (83.9)	14/15 (93.3)	-9.5 (-27.9, 15.9)
12 to 17	32/38 (84.2)	13/18 (72.2)	12.0 (-9.6, 37.5)
Race			
American Indian or Alaska Native	1/1 (100)	0/0 (NA)	NA
Asian	6/7 (85.7)	1/1 (100)	-14.3 (-53.8, 71.8)
Black or African American	3/3 (100)	0/0 (NA)	NA
Native Hawaiian or other Pacific Islander	1/1 (100)	0/0 (NA)	NA
White	35/42 (83.3)	18/23 (78.3)	5.1 (-13.9, 27.6)
Multiple	3/3 (100)	1/1 (100)	0.0 (-63.1, 83.7)
Other	3/3 (100)	2/2 (100)	0.0 (-61.5, 70.6)
Missing	6/9 (66.7)	5/6 (83.3)	-16.7 (-55.2, 32.5)

Characteristic	Crinecerfont N=69 n/N_s (%)	Placebo N=33 n/N_s (%)	Risk Difference % (95% CI)
Ethnicity			
Hispanic or Latino	7/8 (87.5)	3/3 (100)	-12.5 (-48.8, 49.2)
Not Hispanic or Latino	45/52 (86.5)	19/24 (79.2)	7.4 (-9.5, 28.7)
Missing	6/9 (66.7)	5/6 (83.3)	-16.7 (-55.2, 32.5)
Is in United States			
United States	38/44 (86.4)	14/14 (100)	-13.6 (-26.8, 9.0)
Non-United States	20/25 (80.0)	13/19 (68.4)	11.6 (-14.3, 38.0)
Baseline BMI			
<85 th percentile	22/29 (75.9)	10/13 (76.9)	-1.1 (-25.8, 29.8)
≥85 th percentile	36/40 (90.0)	17/20 (85.0)	5.0 (-11.8, 27.5)
Baseline Tanner stage			
Stage 1 or 2	23/28 (82.1)	12/14 (85.7)	-3.6 (-25.4, 24.9)
Stage 3, 4, or 5	35/41 (85.4)	15/19 (78.9)	6.4 (-12.8, 30.7)
Baseline androstenedione level			
≤ULN	10/12 (83.3)	6/6 (100)	-16.7 (-45.7, 26.5)
>ULN	48/57 (84.2)	21/27 (77.8)	6.4 (-10.3, 26.8)

Source: adae.xpt; Software: R

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: BMI, body mass index; CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects with adverse event; NA, not applicable; N_s, total number of subjects for each specific subgroup and were assigned to that specific arm; ULN, upper limit of normal

13.6.3.10. Exposure-Adjusted Analyses, Trial CAH2006

[Table 68](#) shows exposure-adjusted incidence rates in the double-blind and open-label treatment periods combined, with a higher rate per 100 subject-years in subjects who received crinecerfont. The overall event rate was higher in the placebo group. Headache, fatigue, and abdominal pain could potentially be due to glucocorticoid withdrawal from the lowered glucocorticoid doses. Upper respiratory infection, influenza, and nasal congestion are not likely study-drug-related based on mechanism of action.

Table 68. Exposure-Adjusted Subject Incidence Rates Greater in Subjects Who Received Crinecerfont, Trial NBI-74788-CAH2006, Double-Blind and Open-Label Periods Combined

Preferred Term	Crinecerfont (Rate per 100 Subject-Years)	Placebo (Rate per 100 Subject-Years)
Overall	314	451
Headache	32	11
Upper respiratory infection	15	0
Fatigue	14.5	0
Influenza	14.5	10.5
Abdominal pain	11.5	0
Nasal congestion	10.2	5.2

Source: Adapted from Clinical Study Report NBI-74788-CAH2006, Table 32, p114-115

13.7. Key Safety Review Issues

13.7.1. Potential for Adrenal Insufficiency

Issue

Adrenal insufficiency can occur given crinecerfont's mechanism of action of decreasing pituitary ACTH levels, leading to reduced adrenal androgen levels, and ultimately allowing for a reduction in glucocorticoid dose. Acute adrenal insufficiency as a serious adverse event was observed in both Trials CAH3003 and CAH2006.

Background

Glucocorticoid deficiency is a clinical feature of CAH and requires replacement glucocorticoid therapy. Additional glucocorticoid is often needed to lower adrenal androgen levels into the recommended goal range. By reducing elevated adrenal androgen levels, crinecerfont may allow for a reduction in glucocorticoid dose to more physiologic levels. Adrenal insufficiency could occur if the glucocorticoid dose is reduced too much or if an inadequate glucocorticoid dose is given at times of stress.

Assessment

We devised and performed a customized grouped query of preferred terms that could potentially signal acute adrenocortical insufficiency for the double-blind treatment periods of both Trials CAH3003 and CAH2006. Results are shown in [Table 69](#) and [Table 70](#) below.

In Trial CAH3003, adverse events in the adrenal insufficiency grouped query occurred at a greater frequency in the crinecerfont group (43%) compared to the placebo group (27%) (see [Table 69](#)). In contrast, in Trial CAH2006, adverse events in the grouped query occurred at a greater frequency in the placebo group (42%) compared to the crinecerfont group (36%). (see [Table 70](#)).

Time of onset of events in the adrenal insufficiency grouped query is shown in the figures below ([Figure 22](#) and [Figure 23](#)). The pattern of time to onset is similar between crinecerfont and placebo groups in both Trials CAH3003 and CAH2006.

This grouped query search has important limitations. First, most of the preferred terms are nonspecific and may not necessarily reflect adrenal insufficiency. Second, it is possible some of these symptoms could be related to a reduction in the glucocorticoid dose in subjects who are not adrenally insufficient. Third, these symptoms could occur noncontemporaneously, and therefore could reflect different clinical entities at different timepoints. Given these limitations, we next focus on an analysis of specific preferred terms of adrenal insufficiency.

Table 69. Adverse Events Assessment of Adrenal Insufficiency (Grouped Query), Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Grouped Query Preferred Term	Crinecerfont N=122 n (%)	Placebo N=59 n (%)	Risk Difference % (95% CI)
Adrenal insufficiency (GQ)	52 (42.6)	16 (27.1)	15.5 (0.4, 29.0)*
Fatigue	30 (24.6)	9 (15.3)	9.3 (-3.8, 20.6)
Dizziness	10 (8.2)	2 (3.4)	4.8 (-4.0, 11.8)
Decreased appetite	5 (4.1)	1 (1.7)	2.4 (-5.2, 7.9)
Myalgia	5 (4.1)	1 (1.7)	2.4 (-5.2, 7.9)
Adrenocortical insufficiency acute	2 (1.6)	0	1.6 (-4.5, 5.8)
Hyponatraemia	2 (1.6)	0	1.6 (-4.5, 5.8)
Hypotension	2 (1.6)	0	1.6 (-4.5, 5.8)
Lethargy	2 (1.6)	0	1.6 (-4.5, 5.8)
Loss of consciousness	1 (0.8)	0	0.8 (-5.3, 4.5)
Salt craving	1 (0.8)	0	0.8 (-5.3, 4.5)
Mineralocorticoid deficiency	3 (2.5)	1 (1.7)	0.8 (-6.7, 5.6)
Abdominal pain	4 (3.3)	2 (3.4)	-0.1 (-8.6, 5.4)
Nausea	10 (8.2)	5 (8.5)	-0.3 (-10.9, 7.7)
Dizziness postural	1 (0.8)	1 (1.7)	-0.9 (-8.3, 3.0)
Adrenal insufficiency	0	1 (1.7)	-1.7 (-9.0, 1.4)
Hyperkalaemia	0	1 (1.7)	-1.7 (-9.0, 1.4)
Orthostatic hypotension	0	1 (1.7)	-1.7 (-9.0, 1.4)
Blood sodium decreased	1 (0.8)	2 (3.4)	-2.6 (-10.8, 1.7)
Vomiting	6 (4.9)	5 (8.5)	-3.6 (-13.9, 3.7)
Maximum severity			
Death	0	0	0.0 (-6.1, 3.1)
Life-threatening	0	0	0.0 (-6.1, 3.1)
Severe	0	0	0.0 (-6.1, 3.1)
Moderate	18 (14.8)	7 (11.9)	2.9 (-9.0, 12.6)
Mild	34 (27.9)	9 (15.3)	12.6 (-0.7, 24.0)
Serious	1 (0.8)	0	0.8 (-5.3, 4.5)
Deaths	0	0	0.0 (-6.1, 3.1)
Resulting in discontinuation	1 (0.8)	0	0.8 (-5.3, 4.5)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

Relatedness is determined by investigator.

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event

Table 70. Adverse Events Assessment of Adrenal Insufficiency (Grouped Query), Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Grouped Query Preferred Term	Crinecerfont N=69 n (%)	Placebo N=33 n (%)	Risk Difference % (95% CI)
Adrenal insufficiency (GQ)	25 (36.2)	14 (42.4)	-6.2 (-26.4, 13.4)
Abdominal pain	6 (8.7)	0	8.7 (-2.1, 17.8)
Fatigue	5 (7.2)	0	7.2 (-3.5, 15.9)
Decreased appetite	1 (1.4)	0	1.4 (-9.1, 7.8)
Lethargy	1 (1.4)	0	1.4 (-9.1, 7.8)
Muscular weakness	1 (1.4)	0	1.4 (-9.1, 7.8)
Retching	1 (1.4)	0	1.4 (-9.1, 7.8)
Nausea	4 (5.8)	2 (6.1)	-0.3 (-14.4, 9.3)
Myalgia	1 (1.4)	1 (3.0)	-1.6 (-14.1, 5.2)
Blood sodium decreased	0	1 (3.0)	-3.0 (-15.4, 2.4)
Malaise	0	1 (3.0)	-3.0 (-15.4, 2.4)
Dizziness	4 (5.8)	3 (9.1)	-3.3 (-18.4, 7.0)
Vomiting	10 (14.5)	10 (30.3)	-15.8 (-34.5, 0.7)
Maximum severity			
Death	0	0	0.0 (-10.5, 5.3)
Life-threatening	0	0	0.0 (-10.5, 5.3)
Severe	0	0	0.0 (-10.5, 5.3)
Moderate	5 (7.2)	4 (12.1)	-4.9 (-20.9, 6.5)
Mild	20 (29.0)	10 (30.3)	-1.3 (-21.1, 16.5)
Serious	0	2 (6.1)	-6.1 (-19.7, -0.5)*
Deaths	0	0	0.0 (-10.5, 5.3)
Resulting in discontinuation	2 (2.9)	0	2.9 (-7.7, 10.0)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

Relatedness is determined by investigator.

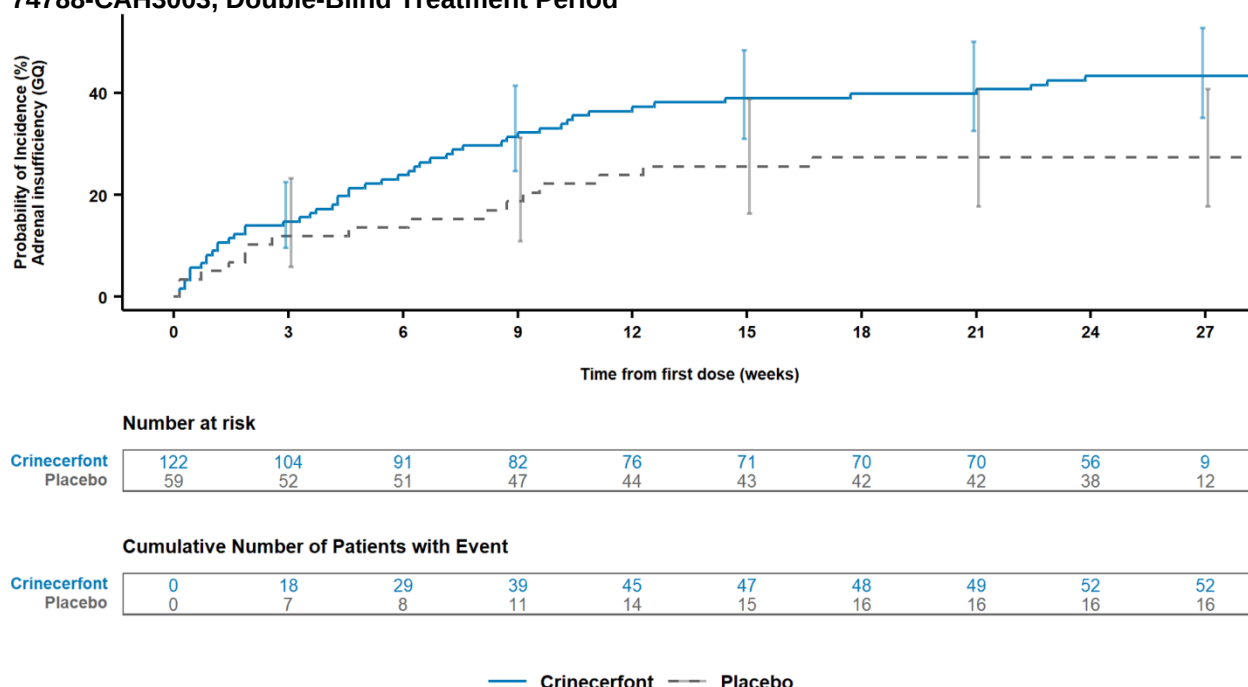
Abdominal pain replaces: Abdominal pain upper

Myalgia replaces: Pain

Asterisk (*) indicates that 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; GQ, grouped query; N, number of subjects in treatment arm; n, number of subjects with adverse event

Figure 22. Time to Onset of Adrenal Insufficiency (Grouped Query), Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



Source: adsl.xpt and adae.xpt; Software: R

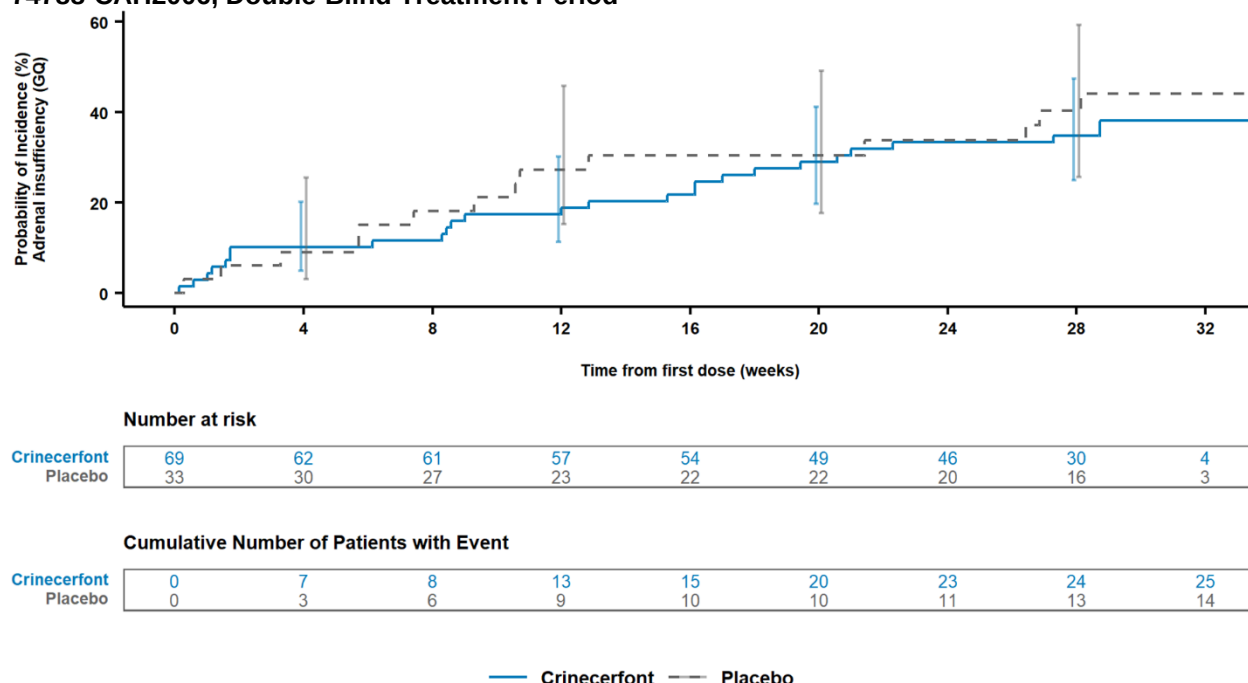
Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 24 weeks.

This figure depicts Kaplan-Meier estimates of the cumulative percentage of subjects who experience an incident (i.e., first) event by a given time point.

Abbreviations: AE, adverse event; GQ, grouped query

Figure 23. Time to Onset of Adrenal Insufficiency (Grouped Query), Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period



Source: adsl.xpt and adae.xpt; Software: R
Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.
Duration is 28 weeks.
This figure depicts Kaplan-Meier estimates of the cumulative percentage of subjects who experience an incident (i.e., first) event by a given time point.
Abbreviations: AE, adverse event; GQ, grouped query

The Applicant provided narratives for all treatment-emergent adverse events with the preferred terms adrenocortical insufficiency acute and adrenal insufficiency. None were likely drug-related. In almost all cases, the adrenal crisis was precipitated by an acute illness and was not adequately treated with stress-dose steroids.

The only case of an adrenal crisis not precipitated by an acute illness was one subject in the placebo group of Trial CAH3003, who experienced an adrenal crisis during the double-blind period after stopping her maintenance hydrocortisone upon advice of her endocrinologist (not a study investigator) because she was thought to be on study drug. This endocrinologist erroneously assumed that crinecerfont treated all aspects of CAH, including the adrenal insufficiency. This case illustrates the importance of ensuring patients and healthcare professionals know to continue at least replacement doses of glucocorticoid therapy while taking crinecerfont as adjunct therapy to reduce residual androgen excess.

Of the eight subjects experiencing an adrenal crisis in Trial CAH3003 while taking crinecerfont, all episodes were secondary to an acute illness coupled with lack of adequate stress-dose steroid. Two episodes of adrenal crisis occurred during the double-blind treatment period, two in the open-label treatment period, and four in the open-label extension beyond Month 12. One subject died from his adrenal crisis in the open-label extension period.

Similarly, the two subjects with narratives related to adrenal crisis while taking crinecerfont in Trial CAH2006 had episodes secondary to acute illness coupled with lack of adequate stress-

dose steroid. One episode of adrenal crisis occurred during the open-label treatment period, and one occurred during the open-label extension beyond Month 12. One subject in Trial CAH3003 experienced a serious TEAE of presyncope during the glucocorticoid reduction period, which is potentially related to glucocorticoid withdrawal (see Section [13.6.2.3](#)).

Conclusion

In conclusion, adrenal insufficiency does not appear to be drug-related but rather related to the underlying disease process of CAH, for which glucocorticoid deficiency is a prominent clinical feature. The adrenal insufficiency case narratives highlight the importance of continuing physiologic replacement glucocorticoid, not decreasing the glucocorticoid below physiologic replacement levels, and taking appropriate stress-dose steroids during times of illness. One case illustrates the importance of ensuring that healthcare professionals know that crinecerfont is adjunctive therapy to at least replacement doses of glucocorticoid therapy.

Action Taken

- Added the description of crinecerfont as adjunctive therapy to physiologic glucocorticoid replacement in the indication statement
- Ensured directions in the Prescribing Information state not to decrease the glucocorticoid dose below physiologic replacement levels
- Ensured directions in the Prescribing Information state that stress-dose glucocorticoid continues to be necessary during acute illnesses and other situations of increased need
- Added directions for timing of monitoring of androstenedione levels after initiation of crinecerfont so the glucocorticoid dose can be evaluated at appropriate time periods

13.7.2. Potential for Hypersensitivity

Background

Throat tightness, perioral edema, and generalized rash (coded as angioedema) occurred in one subject in a phase 1 study (NBI-74788-1724) of crinecerfont in healthy subjects, prompting closer evaluation of potential hypersensitivity events in the phase 3 studies of crinecerfont for the treatment of CAH. The event of angioedema occurred after 3 days of crinecerfont treatment with 100 mg qAM plus 150 mg qPM.

Assessment

To capture potential hypersensitivity events, we examined narrow FMQs within the “immune system disorders” and “skin and subcutaneous tissue disorders” system organ class (SOC). The narrow FMQs (and also the preferred terms) “anaphylactic reaction” and “hypersensitivity” fall under the “immune system disorders” SOC.

During the double-blind treatment period of Trial CAH3003, narrow FMQs within the “skin and subcutaneous tissue disorders” SOC occurred more frequently (and with similar frequency) in the placebo group (12%) compared to the crinecerfont group (11%) during the double-blind period ([Table 71](#)). There were no reported AEs within the narrow FMQs in the “immune system disorders” SOC in either group during the double-blind treatment period of Trial CAH3003.

Table 71. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

System Organ Class FMQ (Narrow)	Crinecerfont N=122 n (%)	Placebo N=59 n (%)	Risk Difference % (95% CI)
Skin and subcutaneous tissue disorders (SOC)	13 (10.7)	7 (11.9)	-1.2
Pruritus	2 (1.6)	0	1.6 (-4.5, 5.8)
Urticaria	1 (0.8)	0	0.8 (-5.3, 4.5)
Alopecia	0	1 (1.7)	-1.7 (-9.0, 1.4)
Rash	10 (8.2)	6 (10.2)	-2.0 (-13.0, 6.4)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

See the table "Patients With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)..."

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

One Trial CAH3003 subject experienced a rash during the double-blind treatment period (Study Day 166) that led to study drug discontinuation. The rash was not likely study-drug-related because skin findings remained present months after study drug discontinuation (see Section [13.6.2.4.1](#) for additional details).

In the open-label treatment period of Trial CAH3003, events of anaphylaxis, bullous dermatitis, and urticaria led to study drug discontinuation. None of the events were likely study-drug-related. The anaphylactic reaction occurred in a subject with a history of a tree nut allergy and exposure to tree nuts. Bullous dermatitis (rash with bullous eruptions) was reported in a subject on Study Day 76 and resolved after about 1 week without treatment or effect on study drug administration. Urticaria occurred on Study Day 197 and the skin findings were still present 1 month after study drug discontinuation. See Section [13.6.2.4.2](#) for additional details.

During the double-blind treatment period of Trial CAH2006, narrow FMQs of "hypersensitivity" and "rash" occurred more frequently in the crinecerfont group versus placebo group (3% versus 0 for "hypersensitivity" and 4% versus 3% for "rash"). However, the two events of "hypersensitivity" consisted of a reaction to a cat and occurred in the same subject ([Table 72](#)). There were no hypersensitivity-related serious AEs or TEAEs that led to study drug discontinuation in Trial CAH2006.

Table 72. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

System Organ Class FMQ (Narrow)	Crinecerfont N=69 n (%)	Placebo N=33 n (%)	Risk Difference % (95% CI)
Immune system disorders (SOC)			
Hypersensitivity	2 (2.9)	0	2.9 (-7.7, 10.0)
Skin and subcutaneous tissue disorders (SOC)			
Rash	3 (4.3)	1 (3.0)	1.3 (-11.4, 9.6)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table. See the table "Patients With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)..."

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

Conclusion

There were no hypersensitivity-related events in the phase 3 studies of crinecerfont for the treatment of CAH that were clearly drug-related. However, labeling regarding the event of angioedema with throat tightness in the phase 1 study is warranted.

Action Taken

Added the hypersensitivity reaction of throat tightness, angioedema, and rash occurring in a subject after 3 days of treatment to Section 5 of the label.

13.7.3. Potential for Neutropenia and Reduction in Total White Blood Cell Count

Background

Neutropenia was observed in a phase 2 study (Study DFI5687) of crinecerfont for major depressive disorder. The pathophysiology of this observation is unclear.

Issue

Decreased neutrophil counts occurred more frequently in study subjects treated with crinecerfont compared to placebo in both Trials CAH3003 and CAH2006. Decrease in mean white blood count over time was also observed in Trial CAH3003 and was more pronounced in the pediatric study.

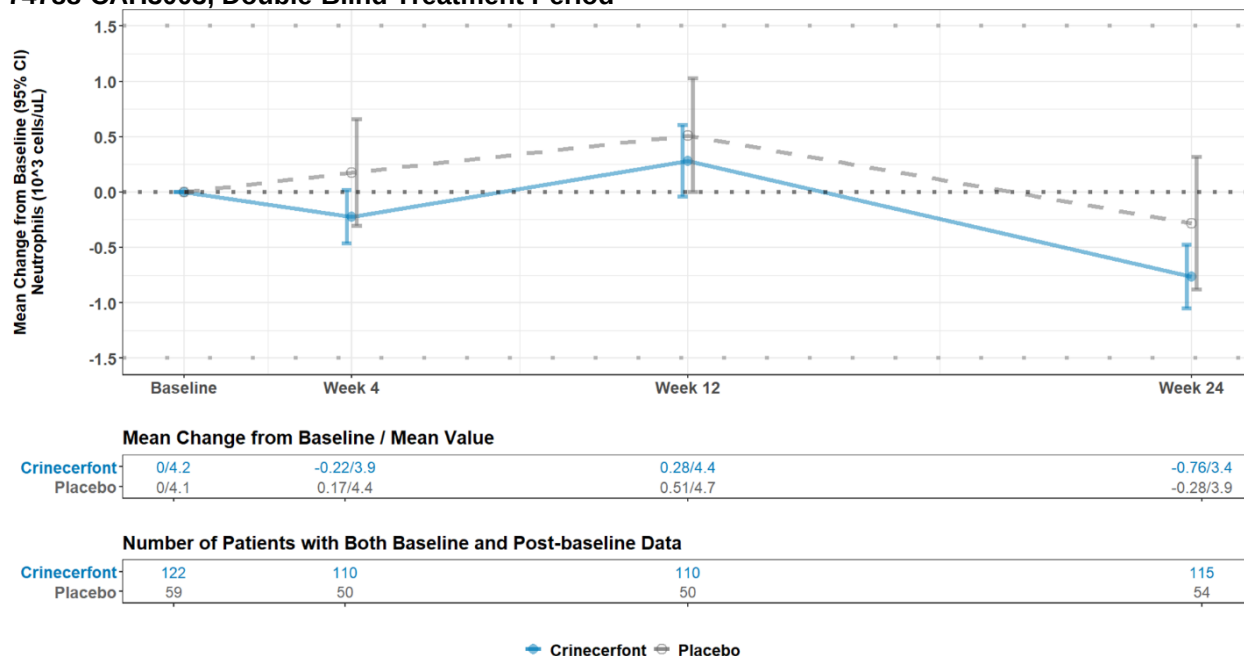
Assessment

In the adult trial (CAH3003), the mean change in neutrophil count was slightly decreased compared to baseline at Week 24 in the crinecerfont group, but the decrease was not notably different from placebo [Figure 24](#).

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Neutrophil counts $<2 \times 10^3$ cells/ μ L (Level 1 abnormality) occurred more frequently in the crinecerfont group (14%) compared to the placebo group (5%) during the 24-week double-blind treatment period of the adult trial (CAH3003), although the incidence of more severe neutrophil count reductions (i.e., $<1 \times 10^3$ cells/ μ L or $<0.5 \times 10^3$ cells/ μ L) was not different between treatment groups (Table 73).

Figure 24. Mean Neutrophil Count Change From Baseline Over Time, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



Source: adlb.xpt; Software: R
Abbreviations: CI, confidence interval

Table 73. Subjects With Neutrophil Values Below Specified Levels, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

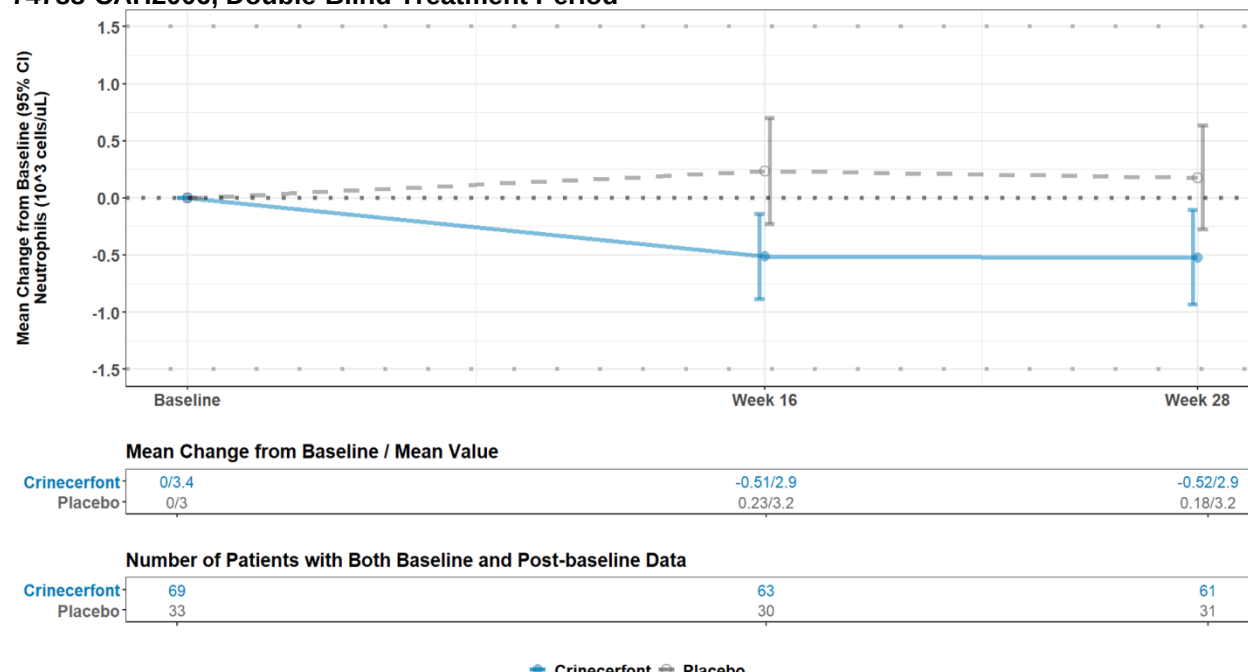
Laboratory Parameter	Crinecerfont N=122 n/N _w (%)	Placebo N=59 n/N _w (%)	Risk Difference % (95% CI)
Neutrophils, low (10^3 cells/ μ L)			
Level 1 (<2)	17/120 (14.2)	3/58 (5.2)	9.0 (-1.2, 17.4)
Level 2 (<1)	1/120 (0.8)	1/58 (1.7)	-0.9 (-8.4, 3.1)
Level 3 (<0.5)	0/120 (0)	0/58 (0)	0.0 (-6.2, 3.1)

Source: adlb.xpt; Software: R
Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications. Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#). Duration is 24 weeks. Risk difference (with 95% confidence interval) is shown between treatment and comparator. In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable. Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

In the pediatric trial (CAH2006), the mean neutrophil count compared to baseline had decreased at Week 16 but had plateaued at Week 28 for both crinecerfont and placebo groups (Figure 25).

The difference in mean change between placebo and crinecerfont is small and unlikely to be clinically meaningful.

Figure 25. Mean Neutrophil Count Change From Baseline Over Time, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period



Source: adlb.xpt; Software: R

Neutrophil counts $<2 \times 10^3$ cells/ μ L (Level 1 abnormality) occurred more frequently in the crinecerfont group (37%) compared to placebo (16%) during the double-blind treatment period of pediatric Trial CAH2006 ([Table 47](#)).

One subject had a neutrophil count $<0.5 \times 10^3$ cells/ μ L (Level 3 abnormality) that was not likely study-drug-related. The narrative follows:

- The subject was a 13-year-old female with an isolated neutrophil count of 0.02×10^3 cells/ μ L on Study Day 191 (Week 28) documented on routine testing. Complete blood count at that visit showed total white blood cell count 3.8×10^9 /L (1% neutrophils, 74% lymphocytes, 12% monocytes, 14% eosinophils, 0% basophils), hemoglobin 13.9 g/dL, hematocrit 45%, platelet count 211×10^9 /L. The neutrophil value was considered spurious.

According to the Applicant, a repeat test at a local laboratory on the same day was within normal limits. Routine follow-up complete blood count at Week 32 while the subject remained on crinecerfont showed recovery of neutrophil count to 1.8×10^3 cells/ μ L.

The only reported adverse event experienced by this subject was the nonserious event of “abdominal pain” (preferred term) which began on Day 194 and lasted 4 days.

Table 74. Subjects With Neutrophil Values Below Specified Levels, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=69 n/N _w (%)	Placebo N=33 n/N _w (%)	Risk Difference % (95% CI)
Neutrophils, low (10 ³ cells/μL)			
Level 1 (<2)	25/68 (36.8)	5/32 (15.6)	21.1 (2.0, 36.7)*
Level 2 (<1)	3/68 (4.4)	0/32 (0)	4.4 (-6.6, 12.2)
Level 3 (<0.5)	1/68 (1.5)	0/32 (0)	1.5 (-9.4, 7.9)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

During the open-label treatment periods of both Trials CAH3003 and CAH2006, the frequency of neutrophil counts <2×10³ cells/μL increased when the placebo double-blind group transitioned to crinecerfont, suggesting a possible drug effect. In Trial CAH3003, the frequency increased from 5% in the placebo DB group to 19% in the placebo/crinecerfont group. In Trial CAH2006, the frequency increased from 16% in the placebo DB group to 23% in the placebo/crinecerfont group. See [Table 75](#) and [Table 76](#).

Table 75. Subjects With Low Neutrophil Counts Below Specified Levels, Safety Population, Double-Blind and Open-Label Treatment Periods, Trial NBI-74788-CAH3003

Laboratory Parameter	Crinecerfont (DB) to Crinecerfont (OL) Weeks 24 to 48 N=117 n/N _w (%)	Crinecerfont (DB) Period Weeks 0 to 24 N=122 n/N _w (%)	Placebo (DB) to Crinecerfont (OL) Weeks 24 to 48 N=57 n/N _w (%)	Placebo (DB) Period Weeks 0 to 24 N=59 n/N _w (%)
WBC Differential				
Neutrophils, low (10 ³ cells/μL)				
Level 1 (<2)	19/117 (16.2)	17/120 (14.2)	11/57 (19.3)	3/58 (5.2)
Level 2 (<1)	3/117 (2.6)	1/120 (0.8)	1/57 (1.8)	1/58 (1.7)
Level 3 (<0.5)	0/117 (0)	0/120 (0)	1/57 (1.8)	0/58 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 24 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Abbreviations: DB, double-blind; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OL, open-label; ULN, upper limit of normal; WBC, white blood cell

Table 76. Subjects With Neutrophil Counts Below Specified Levels, Safety Population, Trial NBI-74788-CAH2006, Open-Label and Double-Blind Treatment Periods

Laboratory Parameter	Crinecerfont (DB) to Crinecerfont (OL) Weeks 28 to 52 N=66 n/N _w (%)	Crinecerfont (DB) Period Weeks 0 to 28 N=69 n/N _w (%)	Placebo (DB) to Crinecerfont (OL) Weeks 28 to 52 N=31 n/N _w (%)	Placebo (DB) Period Weeks 0 to 28 N=33 n/N _w (%)
Neutrophils, low (10 ³ cells/μL)				
Level 1 (<2)	25/65 (38.5)	25/68 (36.8)	7/31 (22.6)	5/32 (15.6)
Level 2 (<1)	1/65 (1.5)	3/68 (4.4)	1/31 (3.2)	0/32 (0)
Level 3 (<0.5)	0/65 (0)	1/68 (1.5)	0/31 (0)	0/32 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 28 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Abbreviations: DB, double-blind; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OL, open-label; ULN, upper limit of normal

One subject in Trial CAH3003, during the open-label treatment period, had neutrophil count <0.5×10³ cells/μL. Absolute neutrophil count was 0.3×10³ cells/μL on Study Day 196 (Week 28; this subject started study drug at Week 24 in the open-label extension period and had been on study drug for 4 weeks) with recovery to a neutrophil count of 5.5×10³ cells/μL by Study Day 225. On Study Day 212, a nonserious adverse event of "bronchitis" was reported for this subject. The relationship of bronchitis to the isolated low ANC is unclear, as is the cause of isolated ANC in this subject.

The clinical significance of the increased frequency of low neutrophil counts is unclear. No study subject in either trial discontinued study drug because of neutropenia. The double-blind treatment period safety database was searched for adverse events coding to the FDA medical query infections and infestations SOC. In Trial CAH3003, the incidence of bacterial infection and purulent material was greater in the placebo group than in the crinecerfont group ([Table 77](#)). In Trial CAH2006, there was an increased incidence of bacterial infection and purulent material in the crinecerfont group compared to placebo ([Table 78](#)).

Neutropenia values for subjects experiencing an adverse event preferred term coded to the infections—pathogen unspecified high-level group term in either study were examined. Preferred terms clearly representing viral infection (e.g., coronavirus infection) were excluded. In neither Trial CAH3003 nor Trial CAH2006 did subjects with adverse events of infection during the double-blind treatment period have coincident or antecedent neutropenia noted on routine laboratory assessment.

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Table 77. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

System Organ Class FMQ (Narrow)	Crinecerfont N=122 n (%)	Placebo N=59 n (%)	Risk Difference % (95% CI)
Infections and infestations (SOC)	53 (43)	32 (54)	-11
Viral infection	22 (18.0)	9 (15.3)	2.8 (-10.0, 13.5)
Purulent material	1 (0.8)	1 (1.7)	-0.9 (-8.3, 3.0)
Bacterial infection	9 (7.4)	5 (8.5)	-1.1 (-11.6, 6.8)
Nasopharyngitis	21 (17.2)	17 (28.8)	-11.6 (-25.6, 1.0)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

See the table "Patients With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)..."

Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

Table 78. Subjects With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

System Organ Class FMQ (Narrow)	Crinecerfont N=69 n (%)	Placebo N=33 n (%)	Risk Difference % (95% CI)
Infections and infestations (SOC)	48 (70)	17 (52)	18
Bacterial infection	11 (15.9)	2 (6.1)	9.9 (-5.2, 21.7)
Nasopharyngitis	18 (26.1)	6 (18.2)	7.9 (-10.8, 23.4)
Purulent material	2 (2.9)	0	2.9 (-7.7, 10.0)
Viral infection	16 (23.2)	8 (24.2)	-1.1 (-20.2, 15.4)
Pneumonia	1 (1.4)	1 (3.0)	-1.6 (-14.1, 5.2)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

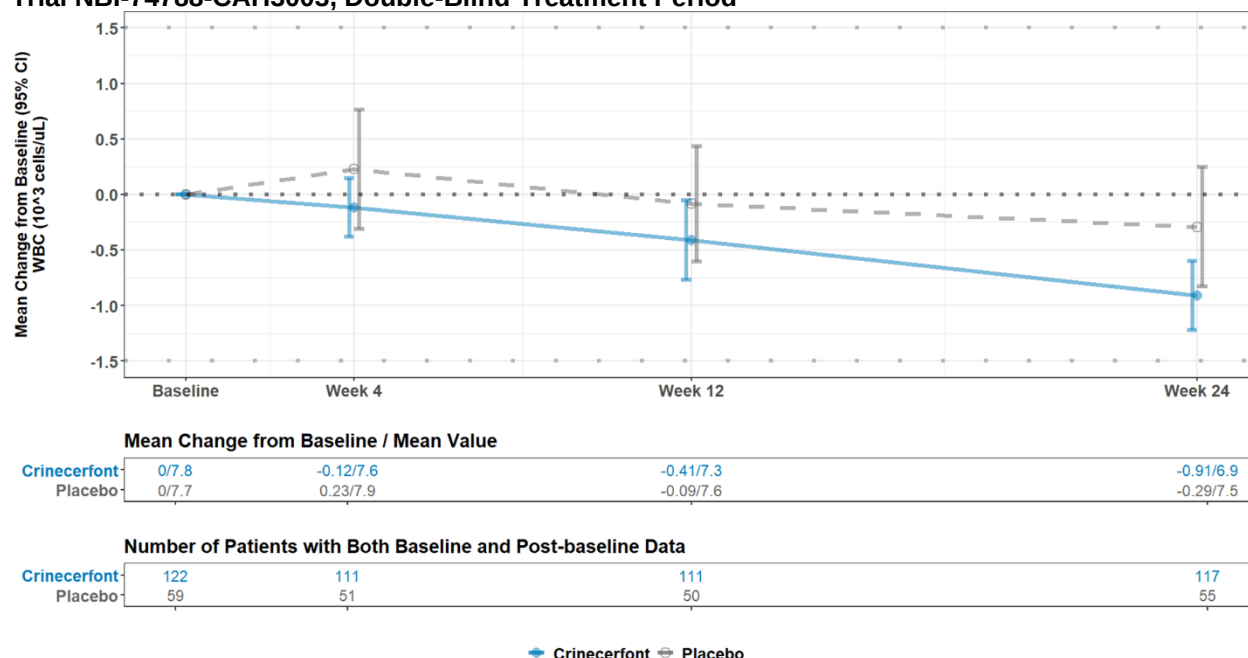
Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

See the table "Patients With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)..."

Abbreviations: CI, confidence interval; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; SOC, system organ class

In Trial CAH3003, the mean white blood cell count decreased from 7.8×10^3 cells/ μ L at baseline to 6.9×10^3 cells/ μ L at Week 24 in the crinecerfont group and from 7.7×10^3 cells/ μ L to 7.5×10^3 cells/ μ L in the placebo group ([Figure 26](#)). There was no notable difference in outlier incidence of low white blood cell counts ([Table 79](#)).

Figure 26. Mean White Blood Cell Count Change From Baseline Over Time, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



Source: adlb.xpt; Software: R
Abbreviations: CI, confidence interval; WBC, white blood cell

Table 79. Subjects With Low White Blood Cell Count Values Below Specified Levels, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=122 n/N _w (%)	Placebo N=59 n/N _w (%)	Risk Difference % (95% CI)
Complete blood count			
WBC, low (10 ³ cells/μL)			
Level 1 (<3.5)	2/121 (1.7)	2/58 (3.4)	-1.8 (-10.2, 3.0)
Level 2 (<3)	0/121 (0)	0/58 (0)	0.0 (-6.2, 3.1)
Level 3 (<1)	0/121 (0)	0/58 (0)	0.0 (-6.2, 3.1)

Source: adlb.xpt; Software: R
Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).
Duration is 24 weeks.
Risk difference (with 95% confidence interval) is shown between treatment and comparator.
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.
Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; WBC, white blood cell

As shown in [Table 80](#), over the 36-month treatment period, the median white blood count ranged from 7.6×10³ cells/μL at baseline to 7.1×10³ cells/μL at Month 36. It is reassuring that the median count did not continue to decline over this exposure period. It is possible that some of the decline is due to reduction in glucocorticoid dose in the crinecerfont-treated subjects. Both acute and chronic treatment with glucocorticoids have been shown to increase peripheral white blood cell count ([Shoenfeld et al. 1981](#)) and it is possible that this slight decline reflects withdrawal of glucocorticoids rather than an effect of crinecerfont itself.

The frequency of white blood cell counts <3.5×10³ cells/μL (Level 1 abnormality) during the open-label treatment period was similar to the frequency in the placebo group during the double-blind treatment period ([Table 81](#)).

Table 80. Median White Blood Cell Count and Change From Baseline for Patients Treated With Crinecerfont, Trial NBI-74788-CAH3003, 36-Month Study Period

Time	N at Time Point	Median White Blood Cell Count ($\times 10^3$ cells/ μ L)	Median Change From Baseline ($\times 10^3$ cells/ μ L) N=122
Baseline	122	7.6	--
Week 4	122	7.4	-0.1
Week 12	122	7	-0.6
Week 24	122	6.5	-0.7
Month 7	104	7.2	-0.6
Month 8	110	7	-0.4
Month 12	108	6.8	-0.7
Month 14	56	7	-0.6
Month 16	42	6.8	-0.9
Month 18	37	6.2	-1.2
Month 24	23	7.5	-0.7
Month 30	10	7.7	-0.3
Month 36	3	7.1	-0.9

Source: Clinical reviewer analysis

Abbreviations: N, number of subjects at time point

Table 81. Patients With Low White Blood Cell Count Values Below Specified Levels, Safety Population, Trial NBI-74788-CAH3003, Open-Label and Double-Blind Treatment Periods

Laboratory Parameter	Crinecerfont (DB) to Crinecerfont (OL) Weeks 24 to 48 N=117	Crinecerfont (DB) Crinecerfont (OL) Weeks 0 to 24 N=122	Placebo (DB) to Crinecerfont (OL) Weeks 24 to 48 N=57	Placebo (DB) Weeks 0 to 24 N=59
	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)
	<i>Complete blood count</i>			
	WBC, low (10 ³ cells/μL)			
Level 1 (<3.5)	4/117 (3.4)	2/121 (1.7)	3/57 (5.3)	2/58 (3.4)
Level 2 (<3)	0/117 (0)	0/121 (0)	1/57 (1.8)	0/58 (0)
Level 3 (<1)	0/117 (0)	0/121 (0)	0/57 (0)	0/58 (0)

Source: adlb.xpt; Software: R

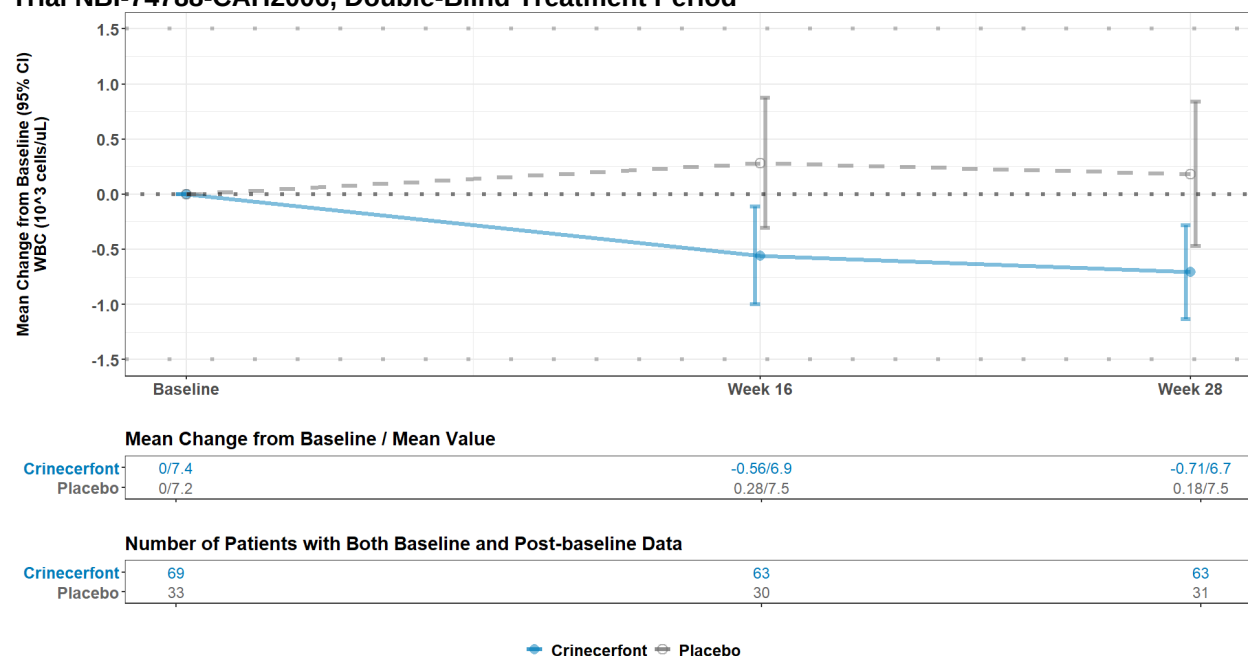
Abbreviations: DB, double-blind; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OL, open-label; ULN, upper limit of normal; WBC, white blood cell

During Trial CAH2006, the mean white blood cell count decreased from 7.4×10^3 cells/ μ L at baseline to 6.7×10^3 cells/ μ L at Week 28 in the crinecerfont group and increased from 7.2×10^3 cells/ μ L to 7.5×10^3 cells/ μ L in the placebo group ([Figure 27](#)).

There was no notable difference in outlier incidence of low white blood cell counts ([Table 82](#)).

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Figure 27. Mean White Blood Cell Count Change From Baseline Over Time, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period



Source: adlb.xpt; Software: R

Abbreviations: CI, confidence interval; WBC, white blood cell

Table 82. Patients With Low White Blood Cell Count Values Below Specified Levels, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=69 n/N _w (%)	Placebo N=33 n/N _w (%)	Risk Difference % (95% CI)
Complete blood count			
WBC, low (10 ³ cells/μL)			
Level 1 (<3.5)	1/68 (1.5)	0/32 (0)	1.5 (-9.4, 7.9)
Level 2 (<3)	0/68 (0)	0/32 (0)	0.0 (-10.8, 5.4)
Level 3 (<1)	0/68 (0)	0/32 (0)	0.0 (-10.8, 5.4)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal; WBC, white blood cell

The median white blood cell count decreased slightly from baseline in the crinecerfont/crinecerfont group through the 52-week study period. The same was not the case, however, for subjects who transitioned from placebo to crinecerfont at Week 28 ([Table 83](#)). It is possible that these observations are due to chance as the sample sizes in Trial CAH2006 were small. No additional subjects experienced a low white blood cell count <3.5×10³ cells/μL during the open-label treatment period ([Table 84](#)).

Table 83. Median White Blood Cell Count and Change From Baseline for Patients, Trial NBI-74788-CAH2006, Double-Blind and Open-Label Study Periods

Time	Crinecerfont/Crinecerfont			Placebo/Crinecerfont		
	N	Median White Blood Cell Count ($\times 10^3$ cells/ μ L)	Median Change From Baseline ($\times 10^3$ cells/ μ L)	N	Median White Blood Cell Count ($\times 10^3$ cells/ μ L)	Median Change From Baseline ($\times 10^3$ cells/ μ L)
Baseline	66	7	--	33	7	--
Week 16	63	6.6	-0.5	30	7.4	0.2
Week 28	63	6.5	-0.4	31	7.4	0.3
Week 40	35	6.4	-0.5	18	7.4	-0.1
Week 52	26	6.1	-0.3	14	7.2	-0.7

Source: clinical reviewer analysis

Abbreviations: N, number of subjects evaluated at each time point

Table 84. Patients With Low White Blood Cell Count Values Below Specified Levels, Safety Population, Trial NBI-74788-CAH2006

Laboratory Parameter	Crinecerfont (DB) to Crinecerfont (OL) Weeks 28 to 52 N=66 n/N _w (%)	Crinecerfont (DB) Weeks 0 to 28 N=69 n/N _w (%)	Placebo (DB) to Crinecerfont (OL) Weeks 28 to 52 N=31 n/N _w (%)	Placebo (DB) Weeks 0 to 28 N=33 n/N _w (%)
	Complete blood count			
WBC, low (10^3 cells/ μ L)				
Level 1 (<3.5)	0/65 (0)	1/68 (1.5)	0/31 (0)	0/32 (0)
Level 2 (<3)	0/65 (0)	0/68 (0)	0/31 (0)	0/32 (0)
Level 3 (<1)	0/65 (0)	0/68 (0)	0/31 (0)	0/32 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 28 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

Abbreviations: DB, double-blind; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; OL, open-label; WBC, white blood cell

To further examine the potential signal of reduction in white blood cells (WBCs) with treatment, laboratory data from the major depression study (Study DFI5687) were reviewed. Adults with major depressive disorder (N=580) were randomized to receive one of three doses of crinecerfont (20 mg, 50 mg, or 100 mg daily), placebo daily, or escitalopram 10 mg daily, for 8 weeks. Median white blood cell count was stable over 8 weeks of treatment in each crinecerfont dose group –median values of 5.8 to 6.0×10^3 cells/ μ L for the 100 mg group, 6.1 to 6.2×10^3 cells/ μ L for the 50 mg group and 5.7 to 6.0×10^3 cells/ μ L for the 20 mg group. In this study, however, subjects received once-daily dosing compared to twice-daily dosing in the CAH studies.

Conclusion

Decreased neutrophil counts ($<2 \times 10^3$ cells/ μ L) occurred more frequently in study subjects treated with crinecerfont compared to placebo during the double-blind treatment periods of both Trials CAH3003 (14% versus 5%) and CAH2006 (37% versus 16%). The frequency increased from 5% in the placebo DB group to 19% in the placebo/crinecerfont group in Trial CAH3003

and from 15.6% in the placebo DB group to 26% in the placebo/crinecerfont group in Trial CAH2006. The clinical significance of these decreased neutrophil counts is unclear, but adverse event data do not suggest an association with increased bacterial infections occurring in children in Trial CAH2006

The reduction in WBCs is more pronounced in children, but in both populations the absolute changes were small, and the absolute values remained within the normal range. Reduced glucocorticoid dose is a possible explanatory factor for the decreased WBCs observed with crinecerfont. The change does not appear to be of clinical significance to treated subjects. Additional postmarketing investigation to evaluate these minor changes in absolute WBC count is unlikely to yield meaningful data that will change the benefit-risk evaluation of crinecerfont. Given that the absolute WBC values stayed in the normal range, we are not requesting the Applicant to include the WBC data in prescribing information.

Action Taken

Added the observation of decreased neutrophil counts to the adverse reactions table in Section 6 (Adverse Reactions) of the Prescribing Information as follows so prescribers are aware that reductions in neutrophils can occur:

Laboratory Findings

- Adults with CAH: Neutrophil count less than 2×10^3 cells/ μ L occurred in 14% (17 of 120) of CRENESSITY-treated subjects, compared to 5% (3 of 58) of subjects in the placebo group. Neutrophil count less than 1×10^3 cells/ μ L occurred in 0.8% (1 of 120) of CRENESSITY-treated subjects, compared to 1.7% subjects (1 of 58) in the placebo group.
- Pediatric subjects with CAH: Neutrophil count less than 2×10^3 cells/ μ L occurred in 37% (25 of 68) of CRENESSITY-treated subjects, compared to 16% (5 of 32) of subjects in the placebo group. Neutrophil count less than 1×10^3 cells/ μ L occurred in 4% (3 of 68) of CRENESSITY-treated subjects, compared to no subjects (0 of 32) in the placebo group.
- We will also request that the Applicant conduct enhanced pharmacovigilance of postmarketing safety data for serious adverse events of bacterial infection and concurrent neutropenia.

13.7.4. Neuropsychiatric Safety Concerns

Issue

A suicide attempt occurred in a Trial CAH3003 subject taking crinecerfont, and more study subjects taking crinecerfont in both Trials CAH3003 and CAH2006 increased their score on the Columbia-Suicide Severity Rating Scale compared to placebo.

Background

The Applicant prospectively identified neuropsychiatric safety as a potential concern because crinecerfont was previously in development as a treatment for depression. The rationale for studying crinecerfont in major depressive disorder was that evidence suggests that CRF1 receptors in the brain mediate CRF-induced anxiety and depression-like behaviors. According to

the Applicant's submission, probes to CRF1 receptors decreased anxiety-like behavior in stressed rats and CRF1 knockout mice showed less anxiety-like behaviors when stressed.

Despite the drug's lack of efficacy in the phase 2 major depressive disorder trial, and limited brain distribution of crinecerfont, the Applicant prospectively monitored for development of suicidality in Trials CAH3003 and CAH2006 using the Columbia-Suicide Severity Rating Scale (C-SSRS).

The Columbia-Suicide Severity Rating Scale (C-SSRS), a validated instrument to assess suicidal ideation and behavior, was administered at screening and at regular intervals during treatment. The C-SSRS consists of a series of six yes/no questions pertaining to suicidal ideation with each question indicating progressively more severe suicidality. The score ranges from 0 (no thoughts of suicide) to 5 (active suicidal ideation with specific plan and intent). See Section [21.3](#) for the C-SSRS questionnaire and scoring.

In Trial CAH3003, the C-SSRS was administered at the following intervals (screening; baseline; Weeks 4, 9, 12, 16, 20, and 24; Months 7, 8, 9, 10, and 12). Subjects with any suicidal behavior within the past year or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) in the 6 months before screening based on the C-SSRS were excluded from the study. These were also study drug discontinuation criteria.

In Trial CAH2006, the C-SSRS was administered at the following intervals to individuals aged ≥ 6 years (screening; baseline; Weeks 4, 16, 28, 40, 52, and 56). Subjects aged ≥ 6 years with a lifetime history of suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) in the 6 months before screening based on the C-SSRS were excluded from the study. These were also study drug discontinuation criteria.

Assessment

To examine a possible relationship between crinecerfont and neuropsychiatric adverse events including suicidality, we searched the safety databases of both trials for events coding to the psychiatric SOC. We also evaluated for subjects who experienced an increase in C-SSRS score (indicating increased suicidality) while on treatment.

Neuropsychiatric Adverse Events

A subject in Trial CAH3003 attempted suicide by taking 19 tramadol tablets and thiocodin while on crinecerfont:

- The serious adverse event of suicide attempt involved a 29-year-old female with a history of acne who had received crinecerfont 100 mg bid starting in the double-blind treatment period and continuing during the open-label treatment period. Concomitant medications administered within 30 days of the event included hydrocortisone and paracetamol/tramadol.

On Study Day 320 (also Day 320 of study drug administration), she was hospitalized after taking 19 tramadol tablets and thiocodin and intentionally injuring her arm. Three days prior to hospital admission the subject had ended a seven-year romantic relationship and as a result, experienced significant deterioration of her mental condition. Computed tomography

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

scanning showed cortical brain atrophy. Study drug was discontinued because of the suicide attempt. The investigator considered the suicide attempt to be unrelated to study treatment.

Another Trial CAH3003 subject discontinued crinecerfont because of restlessness and apathy. His C-SSRS score increased from 0 at baseline to 2 (nonspecific active suicidal thoughts).

A subject in Trial CAH2006 who reportedly discontinued crinecerfont for dizziness, nausea, motion sickness, and retching also experienced anxiety, depression, and suicidal ideation.

Narrow FMQs of the psychiatric SOC occurred more frequently in the placebo group (20.3%) compared to the crinecerfont group (12.3%) in the double-blind period of Trial CAH3003. However, one subject in the crinecerfont group (0.8%) had self-harm and one subject had irritability (0.8%) versus none in the placebo group ([Table 85](#)). In the open-label treatment period, there was one new AE of self-harm in the crinecerfont/crinecerfont group ([Table 86](#)).

Table 85. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

System Organ Class FMQ (Narrow)	Crinecerfont N=122 n (%)	Placebo N=59 n (%)	Risk Difference % (95% CI)
Psychiatric disorders (SOC)	15 (12.3)	12 (20.3)	-8
Irritability	1 (0.8)	0	0.8 (-5.3, 4.5)
Self-harm	1 (0.8)	0	0.8 (-5.3, 4.5)
Depression	4 (3.3)	2 (3.4)	-0.1 (-8.6, 5.4)
Insomnia	4 (3.3)	2 (3.4)	-0.1 (-8.6, 5.4)
Parasomnia	0	1 (1.7)	-1.7 (-9.0, 1.4)
Anxiety	5 (4.1)	7 (11.9)	-7.8 (-18.8, -0.0)*

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

See the table "Patients With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)..."

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

Table 86. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial NBI-74788-CAH3003, Open-Label and Double-Blind Treatment Periods

System Organ Class FMQ (Narrow)	Crinecerfont (DB) to Crinecerfont (OL) Weeks 24 to 48 N=117 n (%)	Crinecerfont (DB) Period Weeks 0 to 24 N=122 n (%)	Placebo (DB) to Crinecerfont (OL) Weeks 24 to 48 N=57 n (%)	Placebo (DB) Period Weeks 0 to 24 N=59 n (%)
Psychiatric disorders (SOC)	10 (8.5)	15 (12.3)	3 (5.3)	12 (20.3)
Anxiety	3 (2.6)	5 (4.1)	1 (1.8)	7 (11.9)
Depression	2 (1.7)	4 (3.3)	1 (1.8)	2 (3.4)
Insomnia	2 (1.7)	4 (3.3)	1 (1.8)	2 (3.4)
Self-Harm	2 (1.7)	1 (0.8)	0	0
Irritability	0	1 (0.8)	0	0
Parasomnia	1 (0.9)	0	0	1 (1.7)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 24 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

See the table "Patients With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)..."

Abbreviations: AE, adverse event; DB, double-blind; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; OL, open-label; PT, preferred term; SOC, system organ class

Narrow FMQs of the psychiatric SOC occurred more frequently in the crinecerfont group (7.2%) compared to the placebo group (3%) in the double-blind period of Trial CAH2006. Anxiety and depression both occurred in two subjects in the crinecerfont group compared to no subjects in the placebo group. (Table 87). In the open-label treatment period, no new events of anxiety or depression occurred (Table 88).

Table 87. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

System Organ Class FMQ (Narrow)	Crinecerfont N=69 n (%)	Placebo N=33 n (%)	Risk Difference % (95% CI)
Psychiatric disorders (SOC)	5 (7.2)	1 (3.0)	4.2
Anxiety	2 (2.9)	0	2.9 (-7.7, 10.0)
Depression	2 (2.9)	0	2.9 (-7.7, 10.0)
Self-harm	1 (1.4)	1 (3.0)	-1.6 (-14.1, 5.2)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

See the table "Patients With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)..."

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; PT, preferred term; SOC, system organ class

Table 88. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Trial NBI-74788-CAH2006, Open-Label and Double-Blind Treatment Periods

System Organ Class FMQ (Narrow)	Crinecerfont (DB) to Crinecerfont (OL) Weeks 28 to 52 N=66 n (%)	Crinecerfont (DB) Period Weeks 0 to 28 N=69 n (%)	Placebo (DB) to Crinecerfont (OL) Weeks 28 to 52 N=31 n (%)	Placebo (DB) Period Weeks 0 to 28 N=33 n (%)
Psychiatric disorders (SOC)	0	5 (7.2)	1 (3.2)	1 (3.0)
Anxiety	0	2 (2.9)	0	0
Depression	0	2 (2.9)	0	0
Self-harm	0	1 (1.4)	0	1 (3.0)
Insomnia	0	0	1 (3.2)	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs not present prior to the initiation of study drug dosing, or already present events that worsened either in intensity or frequency following the initiation of study drug dosing, with an onset on or before the last dose of study drug +28 days.

Subjects in the "Crinecerfont (DB) to Crinecerfont (OL)" arm received crinecerfont in the double-blind treatment period and continued on crinecerfont in the open-label treatment period.

Subjects in the "Placebo (DB) to Crinecerfont (OL)" arm received placebo in the double-blind treatment period and switched to crinecerfont in the open-label treatment period.

Duration is 28 weeks for the double-blind treatment period and 24 weeks for the open-label treatment period.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

See the table "Patients With Adverse Events by Preferred Term Not Captured in FDA Medical Query (Narrow)..."

Abbreviations: AE, adverse event; DB, double-blind; FMQ, FDA medical query; N, number of subjects in treatment arm; n, number of subjects with adverse event; OL, open-label; PT, preferred term; SOC, system organ class

C-SSRS Assessment

A greater proportion of subjects in both Trial CAH3003 and Trial CAH2006 reported any suicidality, measured as any score above zero on the C-SSRS compared to placebo ([Table 89](#)). All study subjects had a baseline score of 0 except for one crinecerfont-treated subject in Trial

CAH3003 who had a baseline score of 1 (wish to be dead). This subject’s score shifted to 0 during the double-blind period.

In Trial CAH3003, three subjects (3/120=2.5%) in the crinecerfont group had a C-SSRS score shift from 0 to a maximum of 2 (nonspecific active suicidal thoughts) versus one subject (1/58=1.7%) in the placebo group during the 24-week double-blind treatment period. Two of the four subjects had a lifetime history of suicidal ideation, one in each group. At baseline, 18 subjects (18/120=15%) in the crinecerfont group versus 6 subjects (6/58=10%) in the placebo group had a lifetime history of suicidal ideation and 3 subjects (3/120=2.5%) in the crinecerfont group versus 2 subjects (2/58=3.4%) in the placebo group had a lifetime history of suicidal behavior. No subjects had an increase in their C-SSRS score during the open-label treatment period as of the data cut-off date.

In Trial CAH2006, four subjects (4/67=6%) in the crinecerfont group versus none (0/31) in the placebo group had a C-SSRS score shift from 0 at baseline to a maximum above 0 during the 28-week double-blind treatment period. Two subjects in the crinecerfont group shifted from a baseline C-SSRS score of 0 to a maximum of 1 (wish to be dead) and two shifted to a maximum of 2 (nonspecific active suicidal thoughts) versus none (0/31) in the placebo group. Two of the four subjects had a lifetime history of suicidal ideation. At baseline, four subjects (4/63=6%) in the crinecerfont group versus none (0/31=0%) in the placebo group had a lifetime history of suicidal ideation. No subjects in either group had a lifetime history of suicidal behavior. During the open-label treatment period, prior to the data cut-off date, one subject shifted their C-SSRS score from 0 at baseline to 3 (active suicidal ideation with any methods [not plan] without intent to act).

Table 89. Subjects Reporting Suicidal Ideation on the Columbia-Suicide Severity Rating Scale, Trials NBI-74788-CAH3003 and NBI-74788-CAH2006, Double-Blind Treatment Period

Trial	Crinecerfont n/N (%)	Placebo n/N (%)
CAH3003	3/120 (2.5%)	1/58 (1.7%)
Max score of 2	3/120 (2.5%)	1/58 (1.7%)
CAH2006	4/67 (6%)	0/31 (0%)
Max score of 1	2/67 (3%)	0
Max score of 2	2/67 (3%)	0

Source: Clinical reviewer-generated table from Applicant’s clinical study report CAH3003 Tables 14.7.1.1.4 and 14.7.1.1.4, and clinical study report CAH2006 Table 15.7.1.1.5

Suicidality measured as any score above zero on the Columbia-Suicide Severity Rating Scale

Crinecerfont dose in Trial NBI-74788-CAH3003 was 100 mg twice daily.

Crinecerfont dose in Trial NBI-74788-CAH2006 was a fixed and weight-based.

In the depression study (DFI5687), subjects with major depressive disorder were randomized to receive 8 weeks of crinecerfont 20 mg daily (n=119), crinecerfont 50 mg daily (n=122), crinecerfont 100 mg daily (n=120), escitalopram 10 mg daily (n=115), or placebo (n=116). One subject receiving crinecerfont 100 mg daily completed suicide after 3 weeks of treatment. There was no suicidal ideation (based on the C-SSRS) dose-response. Suicidal ideation (based on the C-SSRS) occurred at the following rates: escitalopram (15%), placebo (18%), crinecerfont 20 mg daily (27%), crinecerfont 50 mg daily (18%), and crinecerfont 100 mg daily (21%). This trial, however, used daily versus the twice-daily dosing in the CAH trials and did not include children.

The Division of General Endocrinology (DGE) consulted the Division of Psychiatry on October 28, 2024, and the final consult report was checked in to the Document Archiving, Reporting, and

Regulatory Tracking System (DARRTS) on November 25, 2024. The Division of Psychiatry noted the rare incidence of neuropsychiatric and suicidal ideation/behavior events and acknowledged uncertainty in the available clinical trial data. They recommended describing the findings in Section 6 of the prescribing information and including both a description of the suicidal ideation/behavior findings based on the C-SSRS for both adult and pediatric subjects and the suicide attempt that occurred in the open-label extension period of Trial CAH3003.

Conclusion

A serious AE of suicide attempt occurred in a study subject taking study drug. Suicidal ideation, measured by a score above 0 on the C-SSRS, occurred in very few subjects, some of whom had a history of suicidality. The very low event rates significantly limit conclusions, but a suicidality risk cannot be definitively excluded.

Action Taken

Added the following to Section 6.1 (Adverse Reactions) of the label:

Suicidal Ideation and Behavior

- Adults with CAH: Study 1 excluded subjects with active suicidal ideation with intent or plan within the six months prior to screening and those with a history of suicidal behavior within the past year, based on the Columbia-Suicide Severity Rating Scale (C-SSRS) administered at screening. The C-SSRS was administered to subjects at regular intervals during the study. Three of 122 (2.5%) CRENESSITY-treated subjects reported suicidal ideation without method, intent, or plan on the C-SSRS during the 24-week double-blind treatment period compared to 1 of 59 (1.7%) placebo-treated subjects. One of the three subjects receiving CRENESSITY and the placebo treated subject reported a lifetime history of suicidal ideation. One CRENESSITY-treated subject without a history of suicidal ideation or behavior attempted suicide during the open-label period after 320 days of treatment.
- Pediatric subjects with CAH: Study 2 excluded subjects with active suicidal ideation with intent or plan within six months prior to screening or those with a lifetime history of suicidal behavior within the past year, based on the C-SSRS administered at screening. Four of 67 (6%) CRENESSITY-treated subjects and 0 of the 31 (0%) placebo-treated subjects reported suicidal ideation without method, intent, or plan on the C-SSRS during the 28-week double blind treatment period. Two of the four CRENESSITY-treated subjects reported a lifetime history of suicidal ideation. There were no completed suicides or suicide attempts.
- We will also request that the Applicant conduct enhanced pharmacovigilance of postmarketing safety data for serious and non-serious adverse events of suicidal behavior and/or ideation.

14. Therapeutic Individualization

14.1. Intrinsic Factors

Hepatic Impairment

Study NBI-74788-1717 was a phase 1, single-dose, open-label study comparing the PK of crinecerfont in subjects with normal hepatic function (n=6) and mild (n=6), moderate (n=6), and severe hepatic impairment (n=7). All subjects received 100 mg (two 50-mg capsules) crinecerfont with Ensure Plus (350 calories, 11 grams total fat, 20 grams sugars, 13 grams protein, and 50 grams carbohydrate). PK samples were obtained at prespecified time points from predose to 504 hours postdose. Based on the study results, the mean $AUC_{0-\infty}$ was 27%, 34%, and 20% lower in the mild, moderate, and severe hepatic impairment groups, respectively, as compared to the normal hepatic function group. The 90% CI values for the geometric mean ratios (GMRs) for C_{max} , AUC_{tlast} , and $AUC_{0-\infty}$ for all the hepatic impairment groups as compared to the normal hepatic function group included unity ([Table 90](#), see details in [Section 20.2.5](#)). Therefore, we conclude that hepatic impairment does not have a clinically significant impact on crinecerfont PK and agree with the Applicant's proposed labeling that no dose adjustment of crinecerfont is necessary in patients with mild, moderate, and severe hepatic impairment.

Table 90. Crinecerfont GMR and 90% CI PK Parameters Comparing Mild, Moderate, and Severe Hepatic Impairment Groups to Normal Hepatic Function Group Following Single 100 mg Dose

Comparison	$AUC_{0-tlast}$ (ng·hr/mL)		$AUC_{0-\infty}$ (ng·hr/mL)		C_{max} (ng/mL)	
	GMR	90% CI	GMR	90% CI	GMR	90% CI
Mild hepatic impairment vs. normal hepatic function	0.73	0.48, 1.11	0.73	0.48, 1.11	0.91	0.68, 1.22
Moderate hepatic impairment vs. normal hepatic function	0.66	0.43, 1.00	0.66	0.43, 1.00	0.85	0.63, 1.13
Severe hepatic impairment vs. normal hepatic function	0.76	0.50, 1.16	0.80	0.52, 1.21	0.83	0.61, 1.10

Source: Compiled from Table 6, p. 37, Study NBI-74788-1717. [Link to CSR 1717](#).

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-tlast}$, AUC from time zero to time of the last measurable concentration; $AUC_{0-\infty}$, AUC from time zero to infinity; CI, confidence interval; C_{max} , maximum observed plasma concentration; GMR, geometric mean ratio; PK, pharmacokinetic

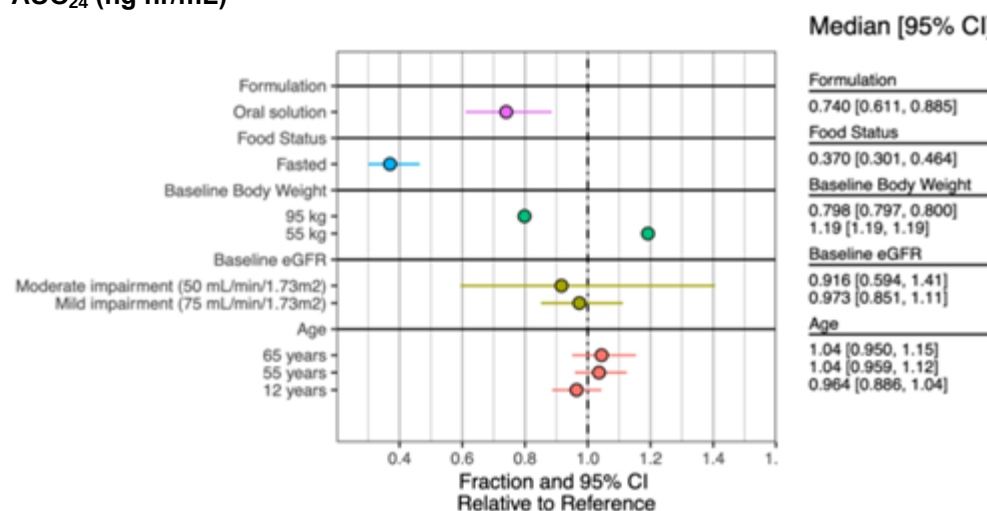
Renal Impairment

The Applicant did not conduct a dedicated renal impairment study. Per the Applicant, the mass balance study (BEX5094) suggested limited renal elimination. In Study BEX5094, a single dose of 100-mg crinecerfont capsule with 2.59 MBq (70 μ Ci) [^{14} C]-crinecerfont was administered with a high-fat breakfast. PK samples were collected at prespecified times from 1- to 3-day intervals through Day 37 postdose. The recovery of radioactivity was not complete by Day 37, and only 49.4% of the administered dose was recovered on average. Of the total amount of radioactivity recovered, 47.3% of the administered dose was recovered in the feces and less than 2% (mainly as metabolites with undetectable crinecerfont) was recovered in the urine (see [Section 20.2.14](#)). Despite the limitations of the mass balance study, considering the negligible amount of crinecerfont in the urine, the review team agrees that renal excretion is unlikely to significantly contribute to the elimination of crinecerfont.

The popPK analysis included estimated glomerular filtration rate (eGFR; Chronic Kidney Disease Epidemiology Collaboration 2009 formula for adult subjects and bedside Schwartz formula for pediatric subjects) as a covariate for crinecerfont clearance. The range of eGFR (indexed to BSA) was evaluated against random effect of crinecerfont apparent clearance (in the base popPK model), and no obvious trend was observed. Additionally, the 95% CI of the eGFR effect on crinecerfont clearance included the null effect of zero, indicating minimal effect of eGFR on crinecerfont PK (refer to Section 20.5). Based on covariate effect assessment shown in Figure 28, the median AUC₂₄ for crinecerfont in subjects with mild and moderate renal impairment were 0.973 and 0.916, respectively of the median crinecerfont AUC₂₄ in subjects with normal renal function. The 95% confidence intervals included 1, indicating no statistically significant impact on crinecerfont AUC₂₄ due to mild to moderate renal impairment. Of note, only a limited number of subjects with moderate renal impairment (n=2, based on BSA-indexed eGFR) in the popPK analysis contributed to a relatively wide 95% CI for the estimated moderate renal impairment impact on crinecerfont AUC (Figure 28).

Overall, mild to moderate renal impairment is unlikely to have clinically meaningful impact on crinecerfont exposure. Therefore, the review team agrees with the proposed labeling that no dose adjustment for crinecerfont is needed in patients with mild or moderate renal impairment. Crinecerfont was not studied in patients with severe renal impairment or end-stage renal disease. According to the FDA's guidance for industry *Pharmacokinetics in Patients With Impaired Renal Function* (March 2024), impaired renal function can be associated with changes in absorption, plasma protein binding, or alterations in some drug metabolism and transport pathways in the liver and gut. These changes can be particularly prominent in patients with severely impaired renal function and those with kidney failure. Considering the potential impact of severe renal impairment on the PK of crinecerfont, and the lack of experience in these patients, the review team recommends avoiding the use of crinecerfont in patients with severe renal impairment and end-stage renal disease.

Figure 28. Forest Plot of Covariate Effects on Crinecerfont Exposure, Steady-State AUC₂₄ (ng·hr/mL)



Source: Applicant's popPK report, Figure 1.1, page 18

Reference subject of 70 kg and 26 years of age with eGFR of 90 mL/min/1.73 m² taking crinecerfont capsules in fed state

Abbreviations: AUC₂₄, area under the concentration-time curve from time zero to 24 hours; CI, confidence interval; eGFR, estimated glomerular filtration rate; popPK, population pharmacokinetics

Other Intrinsic Factors

Based on popPK analysis, no clinically significant differences in the PK of crinecerfont were observed based on age (range: 5 to 54 years), sex (58.7% male), and race (4.8% Asian, 9.7% Black, 77.5% White).

Body weight is a significant PK covariate of crinecerfont. Therefore, weight-band dosing in pediatric patients is proposed to account for the weight impact on crinecerfont PK (refer to Sections [12.1.1](#), [12.1.3](#), and [20.5](#)).

14.2. Extrinsic Factors

Food Effect

Food has a significant impact on crinecerfont absorption. In Study NBI-74788-1736 (n=19), a single dose of crinecerfont 100-mg commercial capsule was administered with a high-fat, high-calorie meal or under fasted conditions. The GMRs for $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} were 3.78, 3.27, and 4.95, respectively, in the fed state compared to the fasted state ([Table 91](#)). A similar magnitude of food effect was observed with earlier capsule formulations (Studies NBI-74788-1712 and NBI-7478-1601, see Sections [20.2.3](#) and [20.2.1](#)).

Table 91. PK Parameters, GMR, and 90% CI of Crinecerfont Following a Single Dose of 100 mg Capsule (Commercial Formulation) Taken Under Fed (High-Fat and High-Calorie Meal) vs. Fasting Conditions

Parameter	Commercial Capsule (Fed Conditions; Test)	Commercial Capsule (Fasted Conditions; Reference)	GMR (90% CI)
	Geometric Mean (CV%)	Geometric Mean (CV%)	
$AUC_{0-t_{last}}$ (ng·hr/mL)	74319 (33.3)	19648 (37.0)	3.78 (3.37, 4.25)
$AUC_{0-\infty}$ (ng·hr/mL)	71594 (26.1)	22073 (33.7)	3.27 (2.87, 3.73)
C_{max} (ng/mL)	4785 (38.6)	967.7 (31.5)	4.95 (4.09, 5.98)

Source: Compiled from Table 11, p.53 and Table 12, p. 59, Study NBI-74788-1736. [Link to CSR 1736](#)

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-t_{last}}$, AUC from time zero to time of the last measurable concentration; $AUC_{0-\infty}$, AUC from time zero to infinity; CI, confidence interval; C_{max} , maximum observed plasma concentration; CV, coefficient of variation; GMR, geometric mean ratio; PK, pharmacokinetic

The food effect of the oral solution was investigated in Study NBI-74788-1734. This was a phase 1, randomized, open-label study in 16 healthy adults who received a single 100-mg dose of oral solution formulation, either with a high-fat, high-calorie meal or under fasted conditions. Data from this study show an approximately 8-fold increase in C_{max} , $AUC_{0-t_{last}}$, and $AUC_{0-\infty}$ in the fed state compared to the fasted state ([Table 92](#), see details under Section [20.2.8](#)).

Table 92. PK Parameters, GMR, and 90% CI of Crinecerfont Following a Single Dose Of 100 mg Oral Solution Taken Under Fed (High-Fat and High-Calorie Meal) vs. Fasting Conditions

Parameter	Oral Solution 100 mg (Fed Conditions; Test)	Oral Solution 100 mg (Fasted Conditions; Reference)	GMR (90% CI)
	Geometric Mean (%CV)	Geometric Mean (%CV)	
AUC _{0-1last} (ng·hr/mL)	65100 (27.7)	9680 (67.1)	8.27 (6.22, 1.10)
AUC _{0-inf} (ng·hr/mL)	67400 (26.9)	10700 (71.5)	8.16 (6.49, 1.03)
C _{max} (ng/mL)	5740 (45.3)	674 (57.9)	8.57 (6.84, 1.07)

Source: Compiled from Table 4, p. 26 and Table 7, p. 29, Study NBI-74788-1734. [Link to CSR 1734](#)

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-1last}, AUC from time zero to time of the last measurable concentration; AUC_{0-inf}, AUC from time zero to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; GMR, geometric mean ratio; PK, pharmacokinetic

Based on significantly enhanced bioavailability of crinecerfont for both oral solution and capsule formulations, pediatric and adult subjects with CAH were instructed to take crinecerfont with breakfast and dinner in the pivotal clinical trials, CAH2006 and CAH3003. Additionally, popPK analysis indicates that fasted status (relative to fed status) has a clinically meaningful reduction in crinecerfont exposure ([Figure 28](#)). Overall, the review team agrees with the proposed labeling that crinecerfont should be administered with food.

Drug Interactions

Crinecerfont as a Victim

Based on in vitro studies, crinecerfont is metabolized primarily by CYP3A4 (fraction metabolized [f_m] ~68 to 74%) and to a lesser extent by CYP2B6 (f_m ~11 to 25%). Crinecerfont is not a substrate for transporters including P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transporting polypeptide (OATP) 1B1, or OATP1B3. Metabolism studies in vitro identified a single active metabolite, M6, with a similar affinity for the CRF1 receptor compared to the parent drug. However, due to limited systemic exposure (i.e., approximately 6% relative to crinecerfont), M6 is not expected to significantly contribute to the pharmacological activity of crinecerfont.

Effect of Strong CYP3A Inhibition on Crinecerfont PK

Study INT5449 evaluated the effect of a strong CYP3A4 inhibitor (ketoconazole) on crinecerfont PK in 16 healthy subjects. In treatment period 1, a single oral dose of 50 mg crinecerfont was administered with a moderate fat breakfast. Following a 22-day washout period, in treatment period 2, ketoconazole 400 mg once daily was administered for 5 days with standardized breakfast, and on Day 6 subjects received ketoconazole 400 mg and 50 mg crinecerfont with a moderate-fat breakfast. Ketoconazole dosing continued from Day 7 to Day 14 of treatment period 2. PK samples were obtained at prespecified time points over 504 hours postdose. The study results show that coadministration with ketoconazole increased crinecerfont AUC and C_{max} by ~45% and ~25% respectively ([Table 94](#), see details in Section [20.2.15](#)). According to the International Council for Harmonisation (ICH) guideline *M12 Drug Interaction Studies* ([May 2024](#)), “Sensitive index substrates are index drugs that demonstrate an increase in area under the concentration versus time curve (AUC) of greater than or equal to 5-fold with strong index inhibitors of a given metabolic pathway in clinical DDI [drug-drug interaction] studies.” Therefore, crinecerfont is not considered a sensitive CYP3A substrate.

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CRENESSITY (crinecerfont) oral capsule and oral solution

In terms of clinical relevance of the DDI, crinecerfont has been studied at daily doses of 300 mg for 28 days, and no major safety concerns were identified. Additionally, in the open-label extension of Trial CAH3003, subjects with CAH who did not have adequate treatment response to crinecerfont were allowed to have a 50% dose increase (e.g., increase from 100 mg bid to 100 mg in the morning and 200 mg in the evening). Therefore, the 45% exposure increase when coadministered with a strong CYP3A4 inhibitor is not expected to fall outside the safety margin seen in the subjects studied and does not necessitate dose adjustment.

Table 93. PK Parameters, GMR, and 90% CI of Crinecerfont When Coadministered With a Strong CYP3A4 Inhibitor (Ketoconazole)

Parameter	Crinecerfont 50 mg	Crinecerfont 50 mg + Ketoconazole 400 mg	GMR (90% CI)
	Geometric Mean (CV%)	Geometric Mean (CV%)	
AUC _{0-tlast} (ng·hr/mL)	17800 (29.0)	25200 (29.0)	1.33 (1.21 to 1.47)
AUC _{0-inf} (ng·hr/mL)	18900 (30.0)	27900 (30.0)	1.45 (1.29 to 1.64)
C _{max} (ng/mL)	1850 (29.0)	2320 (28.0)	1.25 (1.07 to 1.47)

Source: FDA reviewer table from Table 1.1 (Appendix 14.2.5.4.1), p. 539, Table 1.2 (Appendix 14.2.5.4.1), p. 541, and Table 12, p.55, Study INT5449. [Link to CSR](#)

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-tlast}, AUC from time zero to time of the last measurable concentration; AUC_{0-inf}, AUC from time zero to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; CYP, cytochrome P450; GMR, geometric mean ratio; PK, pharmacokinetic

Effect of Strong CYP3A Induction on Crinecerfont PK

Study NBI-74788-1718 investigated the effect of a strong CYP3A4 inducer (rifampin) on crinecerfont PK in 16 healthy subjects. In treatment period 1, a single oral dose of 100 mg crinecerfont was administered with Ensure Plus. Following a 21-day washout period in treatment period 2, subjects received 600 mg rifampin once daily for 29 days in the fasted state. On Day 9 of period 2, subjects received 100 mg crinecerfont 2 hours after rifampin dosing with Ensure Plus. PK samples were obtained at prespecified time points over 504 hours postdose. The study results show that coadministration with rifampin decreased crinecerfont AUC by ~62% and C_{max} by ~23% ([Table 94](#)).

From a clinical perspective, coadministration of crinecerfont with a strong CYP3A4 inducer (rifampin) has a significant impact on the exposure of crinecerfont. Based on the magnitude of exposure reduction, a 2-fold dose increase is necessary to maintain crinecerfont exposure at levels high enough to be effective. The review team agrees with the Applicant's proposed labeling language that crinecerfont dosage should be increased 2-fold (e.g., 200 mg bid in adults) in subjects on concomitant strong CYP3A4 inducers.

Table 94. PK Parameters, GMR, and 90% CI of Crinecerfont When Coadministered With a Strong CYP3A4 Inducer (Rifampin)

Parameter	Crinecerfont 100 mg	Crinecerfont 100 mg + Rifampin 600 mg	GMR (90% CI)
	Geometric Mean (CV%)	Geometric Mean (CV%)	
AUC _{0-tlast} (ng·hr/mL)	37300 (43.9)	13000 (24.8)	0.37 (0.33, 0.42)
AUC _{0-inf} (ng·hr/mL)	38400 (43.8)	13600 (24.1)	0.38 (0.33, 0.43)
C _{max} (ng/mL)	3290 (28.2)	2530 (28.6)	0.77 (0.67, 0.89)

Source: FDA reviewer table from Table 3, p. 37 and Table 4, p.38, Study NBI-74788-1718. [Link to CSR](#)

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-tlast}, AUC from time zero to time of the last measurable concentration; AUC_{0-inf}, AUC from time zero to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; CYP, cytochrome P450; GMR, geometric mean ratio; PK, pharmacokinetic

Effect of Moderate CYP3A Induction on Crinecerfont PK

The Applicant did not conduct any clinical DDI studies with moderate CYP3A4 inducers. In Trial CAH3003, 17 adult subjects were on dexamethasone with or without other glucocorticoids at the time of enrollment. The Applicant considered dexamethasone as a moderate CYP3A inducer (b) (4)

The review team did not agree with the Applicant's approach based on the following considerations. (b) (4)

Despite no observed data to support the dose adjustment for crinecerfont when taken with moderate CYP3A inducers, the review team expects a reduction of less than 50% in crinecerfont exposure due to moderate CYP3A induction, considering that (1) crinecerfont is not a sensitive CYP3A substrate and (2) per the DDI guideline ([May 2024](#)), a moderate CYP3A inducer is defined as decreasing exposure of sensitive CYP3A substrates by 50 to 80%. Thus, the review team recommends that crinecerfont dosage needs to be adjusted in patients taking moderate CYP3A4 inducers. For example, the current dosage of 100 mg twice daily with morning and evening meals should be changed to 100 mg with the morning meal and 200 mg with the evening meal. Increasing the crinecerfont dose by 50% will ensure clinical benefit in this patient population.

Crinecerfont as a Perpetrator

Effect of Crinecerfont on PK of CYP3A Substrates

Study INT6752 investigated the effect of crinecerfont on the PK of midazolam (CYP3A4 probe substrate) in 15 healthy subjects. In treatment period 1, a single oral dose of 2 mg midazolam solution was administered under fasting conditions. Following a 48-hour washout period, crinecerfont 100 mg phase 2 formulation ((b) (4) capsule) was administered once daily with a moderate fat breakfast for 8 days as part of period 2. On Day 8, midazolam was administered 2 hours after crinecerfont. The DDI study shows a 1.23-fold (90% CI: 1.09 to 1.38) increase in midazolam AUC, indicating that crinecerfont is a weak inhibitor of CYP3A4 ([Table 95](#), see [Section 20.2.17](#)). It should be noted that the maximal proposed dose of crinecerfont is 100 mg twice daily, whereas a 100-mg daily dose was used in the DDI study. Based on PK data from Trial NBI-74788-CAH2001, crinecerfont exposure in this DDI study may be about 50% lower than that under the maximal clinical dose. Nonetheless, a more than 2-fold increase in midazolam exposure (a minimal effect to be classified as a moderate CYP3A inhibitor) is not

expected even if the DDI study had been conducted with 100 mg bid. Overall, the review team concludes that crinecerfont is a weak inhibitor at clinically relevant doses.

Table 95. PK Parameters, GMR, and 90% CI of Midazolam With or Without Coadministration of 100 mg Daily Dose of Crinecerfont

Parameter	Crinecerfont 100 mg qd+		GMR (90% CI)
	Midazolam 2 mg	Midazolam 2 mg	
	Geometric Mean (CV%)	Geometric Mean (CV%)	
AUC _{0-tlast} (ng·hr/mL)	21.5 (42)	26.9 (51)	1.23 (1.09 to 1.39)
AUC _{0-inf} (ng·hr/mL)	22.8 (43)	28.5 (53)	1.23 (1.09 to 1.38)
C _{max} (ng/mL)	9.28 (36)	7.70 (31)	0.82 (0.70 to 0.96)

Source: Compiled from Table 15, p. 63 and Table 16 p.65, p.63, Study INT6752. [Link to CSR INT6752](#)

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-tlast}, AUC from time zero to time of the last measurable concentration; AUC_{0-inf}, AUC from time zero to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; GMR, geometric mean ratio; PK, pharmacokinetic; qd, once daily

Study INT11387 investigated the effect of crinecerfont on PK of combined oral contraceptives (COCs, nonsensitive CYP3A substrate per FDA guidance for industry *Clinical Drug Interaction Studies With Combined Oral Contraceptives* ([June 2023](#))) containing ethinyl estradiol and levonorgestrel in 25 healthy subjects. In treatment period 1, subjects were administered Minidril® (0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel) oral tablet for 21 days with food. Following a 7-day washout period, subjects received Minidril oral tablet with crinecerfont 100 mg once per day for an additional 21 days with a moderate fat breakfast. The 90% CI values for the GMR of C_{max} and AUC for both ethinyl estradiol and levonorgestrel, with or without 100 mg crinecerfont, were within the bioequivalence criteria of 0.80 to 1.25, indicating there is no interaction between crinecerfont and ethinyl estradiol- and levonorgestrel-containing oral contraceptives ([Table 96](#), see Section [20.2.16](#)). Similar to Study INT6752 (sensitive CYP3A substrate DDI study), the 100 mg once-daily dose used in this DDI study is lower than the maximal clinical dose of 100 mg twice daily. For Study INT6752, the review team concluded that crinecerfont is a weak CYP3A inhibitor at clinically relevant doses. Based on FDA guidance on drug interactions with COC ([June 2023](#)), weak CYP3A inhibitors are unlikely to cause a clinically significant increase in COC exposures. Therefore, the review team concludes that crinecerfont at clinically relevant doses is not expected to affect the PK of COCs containing ethinyl estradiol and levonorgestrel.

Table 96. PK Parameters, GMR, and 90% CI of Oral Contraceptive Containing Ethinyl Estradiol and Levonorgestrel With or Without 100 mg Daily Dose of Crinecerfont

Parameter	Oral Contraceptive (Ethinyl Estradiol 0.03 mg & Levonorgestrel 0.15 mg)		Crinecerfont 100 mg + Oral Contraceptive		GMR (90% CI)	
	EE	LNG	EE	LNG	EE	LNG
AUC _{0-tlast} (ng·hr/mL)	0.907 (34)	96.5 (31)	0.931 (36)	101 (34)	1.03 (0.98, 1.08)	1.03 (0.98, 1.12)
C _{max} (ng/mL)	0.0713 (35)	6.46 (25)	0.0758 (32)	6.86 (26)	1.06 (1.01, 1.12)	1.06 (1.01, 1.12)

Source: Compiled from Table 15 (p.61), Table 16 (p.63), Table 17 (p.63), and Table 18 (p. 65) Study INT11387. [Link to CSR INT11387](#)

Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; C_{max}, maximum observed plasma concentration; CV, coefficient of variation; EE, ethinyl estradiol; GMR, geometric mean ratio; LNG, levonorgestrel

Effect of Crinecerfont on PK of Glucocorticoids

Glucocorticoids, which are the current standard of care for the treatment of CAH and will be coadministered with crinecerfont in the target patient population, are generally not sensitive CYP3A4 substrates. Based on the study results from the midazolam study (sensitive CYP3A4 substrate) and the oral contraceptive study (nonsensitive CYP3A4 substrate), coadministration with crinecerfont is unlikely to have clinically significant impact on glucocorticoid exposure.

Effect of Crinecerfont on Other CYP Enzymes and Transporters

Crinecerfont is unlikely to induce CYP3A, CYP1A2, CYP2C9, CYP2B6 or inhibit CYP1A2, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP2E1 at clinically relevant doses. Crinecerfont is not an inhibitor of P-gp, BCRP, BSEP, OATP1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 2, multidrug and toxin extrusion transporter (MATE) 1, or MATE2-K.

14.3. Plans for Pediatric Drug Development

The proposed indication includes pediatric patients aged 4 years and older. Because crinecerfont received orphan drug designation, Pediatric Research Equity Act requirements are not triggered by this application and an agreed pediatric study plan is not required.

14.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

The Division of General Endocrinology consulted the Division of Pediatrics and Maternal Health (DPMH) for review of the nonclinical and clinical pregnancy and lactation data, and for recommendations on appropriate language for Section 8 (Use in Special Populations) of the prescribing information based on those data. DPMH also commented on the necessity for postmarketing studies to further evaluate the safety of crinecerfont in the setting of pregnancy and lactation.

Their findings regarding each subsection of Section 8 of the label are discussed below.

Pregnancy

Animal Data

Distribution studies in animals indicated that crinecerfont crosses the placenta and is detected at low levels in fetuses of pregnant rats and rabbits.

Crinecerfont administered during the period of organogenesis in pregnant rats did not result in embryotoxicity or fetal structural malformations at approximately 4 times MRHD exposures. A low incidence of malformations (primarily craniofacial defects) was observed in rabbits at clinically relevant exposures. The incidence of findings in rabbit fetuses was low but exceeded concurrent and historical controls and, therefore, a relationship to crinecerfont cannot be excluded. In a pre- and postnatal developmental toxicity study, no developmental toxicity was observed in rats at 4-fold the MRHD based on exposure.

Human Data

There were three reported pregnancies during the drug development program. One resulted in a spontaneous abortion, one had an unknown outcome, and one was a normal pregnancy.

Details of the three pregnancies are as follows:

- Two pregnancies occurred in the phase 1 study of QT/QTc (corrected QT) evaluations in healthy volunteers, involving single oral doses of 300 mg or 800 mg of crinecerfont, as follows:
 - A 22-year-old female (Subject (b) (6)) was administered a single dose of crinecerfont 300 mg and a single dose of moxifloxacin. She was confirmed to be pregnant during the study based on urine and serum pregnancy tests. The estimated date of conception was approximately 10 days after receiving the single dose of crinecerfont and approximately 1 month after receiving moxifloxacin. Study treatment was discontinued. The subject was subsequently lost to follow-up and no additional information, including additional laboratory assessments or the outcome of the pregnancy, is known.
 - A female of unreported age (Subject (b) (6)) was reported to be pregnant based on positive urine and serum pregnancy tests; however, ultrasound showed no evidence of pregnancy. The subject subsequently had decreasing beta human chorionic gonadotropin levels, consistent with a spontaneous abortion.
- One subject in Trial CAH3003 had a reported pregnancy as follows:
 - A 32-year-old female (Subject (b) (6)) was found to be pregnant (approximately 5 to 6 weeks of gestation) during the open-label period and discontinued crinecerfont on the day that the pregnancy was diagnosed. The subject remained in the study until her Month 18 visit. Subsequently, she underwent an uncomplicated C-section and delivered a healthy infant at 38 weeks of gestation.

Lactation

Animal Data

There were no adverse effects on pre- and postnatal development in developing rats when dams were administered crinecerfont during pregnancy and lactation. Fetuses were exposed to crinecerfont in utero and through lactation until weaning. Crinecerfont was secreted in the milk of lactating rats, with a milk-to-plasma ratio of 1.5 to 12.

Human Data

No cases related to crinecerfont use during lactation occurred during drug development.

Females and Males of Reproductive Potential

Animal Data

There were no effects on mating or fertility in male or female rats treated with crinecerfont prior to mating, with continued treatment in females throughout the early embryonic development period.

Juvenile Animals

The toxicity profile of crinecerfont was determined to be similar between juvenile and adult rats.

Human Data

The clinical data related to changes in hormones related to treatment with crinecerfont are not adequate to inform labeling related to “improved fertility.” Crinecerfont at therapeutic doses is not expected to interfere with efficacy of combined oral contraceptives containing ethinyl estradiol and levonorgestrel.

The Division of Pediatrics and Maternal Health review team provided the following recommendations in their memorandum of consultation filed to NDA 218808 in DARRTS on September 13, 2024:

- In Subsection 8.1 of the label, include a statement that data related to crinecerfont use during pregnancy are insufficient to inform the risks.
- A postmarketing requirement (PMR) for a descriptive pregnancy safety study (DPSS) is warranted.
- In Subsection 8.2 of the label, include that there are no data regarding the presence of crinecerfont in human milk but that because nonclinical data demonstrated that crinecerfont was excreted in animal milk, the drug is likely to be present in human milk.
- Include text in labeling about monitoring infants exposed to crinecerfont through breast milk for signs and symptoms of adrenal insufficiency.
- A PMR for a clinical lactation study to determine the extent to which crinecerfont is present in human milk is warranted.
- Omit [REDACTED] (b) (4)

Additional discussion regarding the rationale for the PMR studies is found in Section [30](#).

15. Product Quality

The Office of Pharmaceutical Quality (OPQ) review team recommends approval of the applications for both dosage forms: oral capsule and oral solution (NDAs 218808 and 218820, respectively).

Capsule

The OPQ review team has assessed NDA 218808 with respect to chemistry, manufacturing, and controls (CMC) and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this NDA from a quality perspective. As part of this action, an expiration period of 15 months for the product, stored at 15°C to 25°C (59°F to 77°F) in the commercial packaging, is granted.

The drug product is a soft gel capsule product of crinecerfont, a synthetic new molecular entity. The proposed product is an immediate-release dosage form. It has not been approved previously.

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

The drug product capsules are produced in three different strengths: 10 mg, 25 mg, and 100 mg.

(b) (4)
In addition to the drug substance, the capsule contains the following excipients, whose functions are listed in parenthesis: medium-chain triglycerides (b) (4) propylene glycol dicaprylate (b) (4) lauroyl polyoxyl-32 glycerides (b) (4) vitamin E polyethylene glycol succinate (b) (4) and the soft gelatin capsule shell. All excipients are controlled to relevant compendial standards. Propylene glycol dicaprylate has not been used in oral formulations previously but has been previously approved for topical products and as a food additive. The container closure system is an opaque high-density polyethylene bottle with a child resistant cap and foil seal.

The capsule manufacturing process (b) (4)

(b) (4)
The manufacturing process is adequately controlled by the quality management system of the listed current good manufacturing practice-compliant manufacturing facilities. From a quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, potency, and stability.

The Applicant is requesting a 15-month shelf life based on the provided long-term (25°C) and accelerated data. The accelerated conditions were reduced from the usual 40°C to 30°C because the soft gel capsule body would deform at the higher temperature regime. Registration batches (soft gel) have 12 months of long-term and accelerated data. Stability data for phase 3 batches (hard gel) up to 15 months is provided as well to support the stability conclusions. Overall, the 15-month shelf life can be granted when the product is stored at 15°C to 25°C (59°F to 77°F). The Applicant commits to place one batch on stability each year that products are manufactured. Exemption from environmental assessment is made and acceptable.

Oral Solution

The OPQ review team has assessed NDA 218820 with respect to CMC and has determined that it meets all applicable standards to support the identity, strength, quality, and purity that it purports. As such, OPQ recommends approval of this NDA from a quality perspective. As part of this action, an expiration period of 18 months for the product, stored under refrigerated conditions at 2°C to 8°C (36°F to 46°F) in the commercial packaging, is granted. Once a bottle is opened for use, it may be stored under refrigeration at 2°C to 8°C (36°F to 46°F) or at room temperature (15°C to 25°C [59°F to 77°F]) for up to 30 days.

Crinecerfont oral solution is available in one strength (50 mg/mL), packaged in a compatible (b) (4) mL polyethylene terephthalate (PET) bottle with child-resistant cap. The drug product is formulated as solution using excipients such as medium-chain triglycerides, (b) (4) butylated hydroxytoluene, saccharin, and orange flavor (b) (4). Other than the orange flavor, all excipients are compendial, controlled by United States Pharmacopeia–National Formulary standards, and are used in amounts within the limits of the FDA’s IID. There are no novel excipients and no excipients of human or animal origin. The drug product manufacturing process is adequately controlled by the quality management system of the listed current good manufacturing practice-compliant manufacturing facilities. All analytical methods for quality control of the product are adequate and they are appropriately validated. Based on the provided stability data, the Applicant’s proposed shelf-life of 18 months is acceptable when stored under

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

long-term refrigerated conditions (2°C to 8°C). From a quality perspective, the proposed control strategies are adequate to ensure consistent product quality with regard to identity, strength, purity, potency, and stability.

15.1. Device or Combination Product Considerations

Not applicable. This is not a combination drug product.

16. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

The Applicant has submitted required financial certification and disclosure. There were no investigators with disclosable information.

The Applicant states that the clinical trials conducted in support of this application were conducted in full compliance with good clinical practice.

The Office of Study Integrity and Surveillance determined that an inspection was not needed for the study site Celerion, Tempe because the Office of Regulatory Affairs had previously conducted an inspection for that site in April 2024, in support of another application, NDA 219008. The Office of Study Integrity and Surveillance concluded that data from the reviewed studies were reliable.

17. Advisory Committee Summary

An advisory committee meeting was not convened for this application because we determined that the application did not raise efficacy, safety, or other issues requiring input from external experts.

III. Additional Analyses and Information

18. Summary of Regulatory History

Crinecerfont (NBI-74788) is a small molecule, selective antagonist of the corticotropin-releasing factor type 1 (CRF1) receptor. Sanofi (formerly Sanofi-Synthelabo, Inc., and then Sanofi Aventis US Inc.) originally developed NBI-74788 (then known as SSR125543) and initiated its clinical development for the treatment of major depressive disorder in May 2005 under IND (b) (4) regulated by the Division of Psychiatry Products. Sanofi withdrew the IND (b) (4) (b) (4) Neurocrine Biosciences, Inc. (Neurocrine) licensed the compound from Sanofi in 2015.

The IND application 132849 was submitted by the Sponsor, Neurocrine, on December 23, 2016, to investigate crinecerfont (NBI-74788) for the treatment for congenital adrenal hyperplasia (CAH) (b) (4). On March 16, 2017, following review of the initial IND, FDA issued nonhold comments and requests for additional information regarding quality, nonclinical, and clinical topics.

On April 16, 2018, a preliminary breakthrough therapy designation (BTD) request teleconference was held. FDA determined it was premature to submit a BTD request and the drug/indication did not meet breakthrough criteria at that stage of development. Three reasons were provided for discouraging the Sponsor from submitting a BTD request at this stage of development:

- CAH is a serious and life-threatening condition because it is associated with adrenal insufficiency; however, the Sponsor's study drug has the potential to decrease androgen levels but does not treat adrenal insufficiency.
- Approved therapies for treatment of CAH exist and are considered standard of care for this disease (e.g., glucocorticoid [GC] and mineralocorticoid replacement drugs).
- There is no evidence to date that the Sponsor's study drug provides a significant clinical benefit over existing therapies. This drug has been shown to decrease levels of a surrogate biomarker, 17-hydroxyprogesterone (17-OHP), in adults with classic CAH in a phase 1b proof-of-concept study. More clinical evidence is needed to demonstrate effects of this drug on a clinically significant endpoint (for example, reduction in GC requirements that will be associated with reduction in frequency or severity of adverse events related to GC overreplacement, or improvement in symptoms related to CAH).

On November 7, 2018, the Sponsor requested a Type C written responses only meeting, to address the Division of General Endocrinology's (DGE's) nonclinical comment regarding new excipients in drug formulations used in the IND-opening study and to obtain agreement on the appropriateness of the drug product formulation proposed for use in the long-duration phase 3 clinical studies and in a commercial setting in adult and pediatric subjects. FDA agreed that the amount of medium-chain triglycerides, lauroyl polyoxylglycerides, and (b) (4) excipients in the proposed formulation present no specific safety concerns for chronic oral use. Also, the Sponsor's proposed excipient propylene glycol dicaprylocaprate (b) (4) and its daily

doses in the formulation appeared to have sufficient scientific nonclinical information available within the publicly available and manufacturer-supplied literature to support safety.

On March 15, 2019, Orphan Drug designation was granted to crinecerfont for the treatment of classic CAH.

On April 24, 2019, the Sponsor submitted a Fast Track designation request. They identified CAH as a serious condition and hypothesized that treatment with crinecerfont may potentially decrease the need for supraphysiologic glucocorticoid regimen to suppress hyperandrogenism in patients with CAH. The request was denied due to the limited data provided from the ongoing phase 2 trial, NBI-74788-CAH2001 (hereafter Trial CAH2001), regarding the potential of crinecerfont to provide a clinically meaningful benefit, or to address an unmet medical need in the patients with CAH population, or to address a serious aspect of CAH. The denial letter was issued on June 20, 2019.

On May 29, 2019, the Sponsor requested a Type C meeting, to discuss and obtain agreement on the nonclinical and clinical development plan to support an NDA for the treatment of CAH. A written response letter was issued, August 12, 2019, to address the Sponsor's questions regarding the proposed product development plans. In brief, DGE communicated agreement that glucocorticoid dose reduction may be clinically beneficial in patients with CAH and that assessment of glucocorticoid dose reduction and control of adrenal steroid hormone levels was an acceptable approach for the planned phase 3 registration study. Also, DGE agreed that the nonclinical program as described in the meeting briefing materials, as well as the number of subjects and duration of exposures in the clinical safety database, were sufficient to support an NDA submission, provided no new safety signals were identified that would require further evaluation.

On January 6, 2020, the Sponsor requested a Type B, end-of-phase 2 meeting, to discuss the design of the pivotal Trial NBI-74788-CAH3003⁸ (hereafter Trial CAH3003), particularly dose selection and the identification of the primary and secondary endpoints and analysis, and the adequacy of the human mass balance study. A teleconference was held on March 17, 2020. During the discussion, DGE confirmed that percent change in glucocorticoid daily dose is the preferred approach for the primary endpoint and accepted the glucocorticoid dose reduction target (to be updated (b) (4) to 8 to 10 mg/m²/day) and the criteria for achieving physiologic glucocorticoid dose (≤ 11 mg/m²/day) in preventing significant study discontinuation due to subjects experiencing adrenal insufficiency. Agreement that androstenedione is an appropriate pharmacodynamic marker was conveyed, but DGE requested that adrenocorticotrophic hormone (ACTH) levels continue to be collected and that morning dosing, as part of a bid regimen, is needed for maximal suppression of excess adrenal androgen production throughout the day. Additional comments were communicated in the meeting minutes issued on May 27, 2020.

On May 13, 2020, the Sponsor requested a Type B meeting to obtain guidance on the plan to develop crinecerfont in the pediatric population. The objectives of this meeting were to gain advice on (1) the appropriateness of pediatric Trial NBI-74788-CAH2006 (hereafter Trial CAH2006) to evaluate the efficacy, safety, and tolerability of crinecerfont to treat classic CAH in patients 2 to 17 years of age, (2) the sufficiency of a safety database consisting of all safety data

⁸ "A Randomized, Double-Blind, Placebo-Controlled Study To Evaluate the Safety and Efficacy of Crinecerfont (NBI-74788) in Adult Subjects With Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment"

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

available from pediatric Trial CAH2006, combined with safety data available from the adult program, to support labeling of crinecerfont to treat classic CAH in pediatric patients, (3) the appropriateness of the strategy to evaluate safety, tolerability, and pharmacokinetic data for crinecerfont in pediatric patients with classic CAH (b) (4) and (4) the acceptability of crinecerfont oral solution for use in pediatric Trial CAH2006 and for the (b) (4). The written responses were issued July 9, 2020.

On April 29, 2021, the Sponsor requested Fast Track designation for the treatment of classic CAH. After review, DGE concluded it met the criteria for the Fast Track designation and issued the granted letter on June 15, 2021.

On June 4, 2021, the Sponsor requested a type C written responses only meeting to obtain guidance on (b) (4) for an ongoing adult pivotal trial, Trial CAH3003, (b) (4)

DGE disagreed with the proposed (b) (4) and conveyed several recommendations. It was also suggested that access to comparative interim results should be limited to individuals with relevant expertise who are independent of the personnel involved in conducting or managing the trial. Written responses were issued on August 3, 2021.

On March 8, 2022, the Sponsor requested preliminary BTDR request advice. A teleconference was held on March 25, 2022, with the Sponsor to discuss the submission. It was determined that the request was premature.

On July 7, 2022, the Sponsor submitted a request for a chemistry, manufacturing, and controls (CMC)-only Type B end-of-phase 2 teleconference. The purpose of this interaction was to obtain concurrence regarding crinecerfont drug substance and drug product manufacturing and stability activities to ensure that meaningful data would be generated to support the submission of an NDA for crinecerfont for the treatment of classic CAH. The Office of New Drugs, Office of Pharmaceutical Quality (OPQ), provided guidance on questions in the written response issued September 12, 2022. A request for clarification was submitted October 4, 2022. A response was issued October 11, 2022, providing clarification on the stability and validation requirements for the drug substance prior to commercial launch.

On July 12, 2022, the Sponsor requested a type C meeting to obtain guidance on the content and planned analyses specified in Trial CAH3003 statistical analysis plan (SAP) and the proposal for the data package from clinical studies conducted by the previous sponsor (Sanofi SA), including data acquired with low-bioavailability formulations in a future NDA submission. DGE provided feedback in written responses issued on September 20, 2022.

On December 7, 2022, the Sponsor requested a type C meeting to discuss the content and planned analyses specified in Trial CAH2006 SAP. Written responses were issued on February 14, 2023.

On May 15, 2023, the Sponsor requested a type D meeting to discuss the proposed supplementary analyses for Trial CAH3003, which were intended to help understand the potential impact of androstenedione (A4) variability on the primary endpoint (as well as the

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

related key secondary endpoint), and whether the tipping point analyses had been sufficiently addressed in the SAP. Written responses were issued on June 21, 2023.

On July 21, 2023, the Sponsor requested a type C meeting (b) (4)

DGE provided general comments as well as responses to their question in the written responses issued on October 3, 2023.

On September 15, 2023, the Sponsor submitted two meeting requests. The Sponsor requested a type B pre-NDA meeting to discuss the proposed NDA contents, statistical analyses, and timeline for an NDA submission. The Sponsor described their plans to seek approval of crinecerfont for the treatment of classic CAH based on the results of Trials CAH3003 and CAH2006 and planned to submit separate NDAs for a proposed soft gelatin capsule (NDA 218808) and oral solution formulation (NDA 218820). The videoconference held on November 15, 2023, discussed (1) proposed nonclinical and clinical packages for the planned crinecerfont NDA submission, (2) organization and content of Modules 2.7.3 Summary of Clinical Efficacy and 2.7.4 Summary of Clinical Safety for the NDA submission, (3) proposed plan for the assessment of abuse liability, (4) proposed population pharmacokinetics (popPK) and exposure-response analyses, (5) available safety database at the time of the planned NDA submission, (6) content and organization of the 120-Day Safety Update, and (7) proposed content and format of the crinecerfont NDA constituting a fileable marketing application. Additional comments were captured in the meeting minutes issued on December 8, 2023.

A separate type B, CMC-only pre-NDA meeting was submitted to review the proposed CMC content to support a new drug application submission for crinecerfont. Feedback was provided in the written responses issued November 14, 2023. On November 30, 2023, the Sponsor submitted a request for clarification. OPQ provided a response concerning dissolution testing on their drug production in the advice letter issued on December 20, 2023.

On October 11, 2023, the Sponsor submitted a BTM request. DGE determined the revised agreed upon indication met the criteria for BTM. Therefore, BTM was granted for crinecerfont for the treatment of classic CAH in the letter issued December 1, 2023.

On April 29, 2024, and April 30, 2024, Neurocrine submitted two NDAs for crinecerfont capsules and oral solution, respectively, (b) (4)
Crinecerfont is a new molecular entity and the review classification for these applications is “priority.”

19. Pharmacology Toxicology

19.1. Summary Review of Studies Submitted With the Investigational New Drug Application

Crinecerfont is a selective antagonist of CRF1 receptors. Crinecerfont blocks the binding of CRF to CRF1 receptors in the pituitary but not to CRF2 receptors. Studies in the nonclinical program to support crinecerfont clinical studies were conducted with different salt forms of crinecerfont. The primary pharmacology studies were mainly conducted with crinecerfont hydrochloride

(HCl). The initial pharmacokinetic (PK) and toxicology studies were conducted with the tosylate salt form. Because of the low absorption and a large food effect in clinical studies, different formulations of crinecerfont tosylate salt and free base forms were evaluated in absorption studies. The free base (b) (4) formulation was selected for later nonclinical and clinical studies (b) (4)

Nonclinical studies adequately bridged the data from studies conducted with tosylate salt to those conducted with the free base, and both sets of studies contributed to characterizing the toxicity profile of crinecerfont.

19.1.1. ADME / PK

Crinecerfont absorption, distribution, metabolism, and excretion (ADME) and PK parameters were characterized in a series of in vitro and in vivo studies. In vivo studies were conducted in rat, dog, mouse, rabbit, and monkeys. The nonclinical PK studies are summarized below.

Absorption

Crinecerfont absorption and pharmacokinetics were evaluated in vitro and in nonclinical species using intravenous (IV) and oral administration of crinecerfont. An in vitro study in colorectal adenocarcinoma (Caco)-2-TC7 cells with [¹⁴C]-crinecerfont tosylate showed that crinecerfont membrane permeability was low and that crinecerfont was not a substrate for P-glycoprotein (P-gp) transporter. Single-dose in vivo PK studies were conducted with tosylate salt and free-base crinecerfont following oral (PO) or IV administration. Bioavailability from oral dosing was 53% in rats, 14% in rabbits, and 19% in dogs for tosylate salt, and 49% in monkey for free base. Absorption was higher for free-base crinecerfont in (b) (4) formulation and when administered with food. The half-life ($t_{1/2}$) of crinecerfont following single oral or IV administration was 8 hours in mice, 13 to 24 hours in rat, 8 hours in rabbits, 24 to 90 hours in dogs, and 5 to 13 hours in monkeys. The time to reach maximum observed plasma concentration (T_{max}) following a single oral administration of crinecerfont tosylate ranged from 2 to 6 hours. In general, exposure of crinecerfont increased less than dose-proportionally and approached saturation or plateaued as dose increased. In repeated-dose toxicokinetic (TK) analyses in toxicity studies, no accumulation was observed in rats when crinecerfont was administered as the tosylate salt. Modest accumulation was observed for free base administered as (b) (4) at 5, 15, and 50 mg/kg/day doses (less than 3-fold accumulation), with a decrease in exposure observed at the high dose after repeat doses. Exposure was not sex-dependent in rats, but exposure was slightly higher in female dogs compared to males (<2-fold).

Distribution

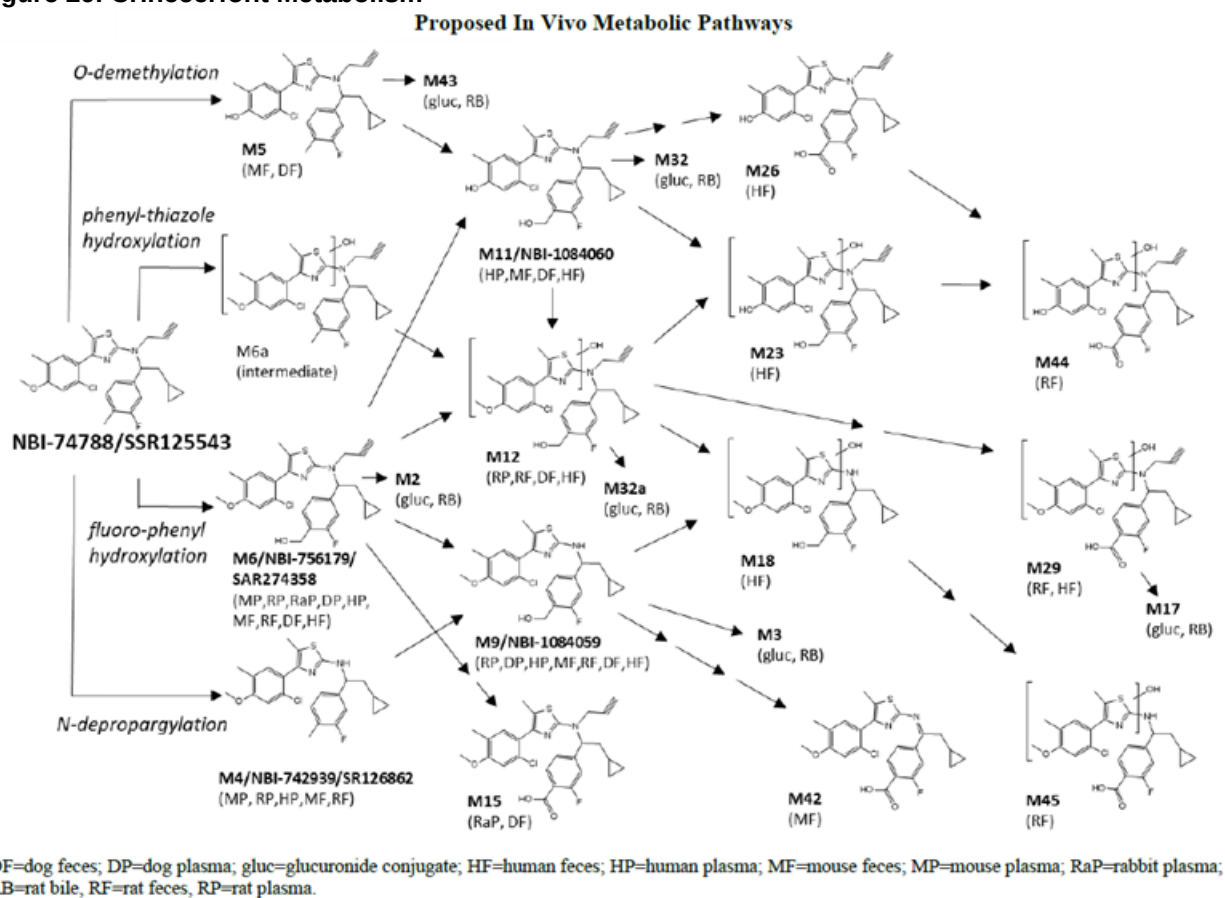
Crinecerfont distribution was evaluated in in vitro and in vivo studies, including by whole-body imaging, tissue distribution and placenta transfer studies. In in vitro binding assays, crinecerfont exhibited high plasma protein binding with $\geq 99.9\%$ bound in mouse, rat, rabbit, and human plasma independent of drug concentration. Distribution to blood cellular components was low, with blood cell-to-plasma ratios of 0.18 in mouse, 0.17 in rat, 0.14 in dog and 0.08 in human. In vivo studies in rat and dog demonstrated that there was no significant binding of crinecerfont to erythrocytes. Crinecerfont was widely distributed in liver, adrenal gland, lung, spleen, myocardium, fat, and the lymphatic system in tissue distribution studies after oral or IV

administration. Crinecerfont crossed the placenta and distributed to the fetal liver (at low levels) in pregnant rats and rabbits. Low crinecerfont exposure was observed in brain, skin, and testis. The brain-to-plasma exposure ratio in rat was 0.1 compared to the liver-to-plasma exposure ratio of ≥ 8.5 .

Metabolism

The metabolism of crinecerfont was evaluated in vitro using liver microsomes and hepatocytes and in vivo in mouse, rat, rabbit, dog, and monkey. The metabolism of crinecerfont was similar among species, with no unique or disproportionate human metabolites (Figure 29). Crinecerfont was primarily biotransformed by phase 1 metabolism (hydroxylation of the fluorophenyl moiety and N-depropargylation) by cytochrome P450 (CYP) 3A4, and to a lesser extent by CYP2B6. The most abundant metabolite, M6 (NBI-756179), was formed by hydroxylation of the fluorophenyl moiety and represented 6% of human crinecerfont exposure. M6 bound to CRF1 receptors with nanomolar affinity ($K_i=1.14\text{nM}$), which, coupled with a relatively slow dissociation rate of 0.01 min^{-1} , resulted in a relatively longer receptor residence time ($t_{1/2}$ of ~63 minutes). Due to its low abundance, the contribution of M6 to CRF1 receptor antagonist activity was considered minor. In vitro studies showed crinecerfont exhibited low potential for drug-drug interaction (DDI) based on limited evidence of inhibition or induction of CYP enzymes or drug transporters.

Figure 29. Crinecerfont Metabolism



Source: Module 2.6.4 PK Written Summary of the NDAs

Excretion

Crinecerfont excretion studies were conducted in mouse, rat, and dog using [¹⁴C]-crinecerfont tosylate. Crinecerfont was mainly excreted through feces in mouse, rat, and dog, indicating clearance mainly through hepatobiliary system. Renal excretion was negligible (<2%). The elimination rate of crinecerfont was slow. The recovery of an orally administered dose of [¹⁴C]-crinecerfont was not complete at 1 week in rats, with about 10% of radioactivity remaining in the tissues in males and 25% in females. In a dog study, 80% of [¹⁴C]-crinecerfont administered orally was recovered at 2 weeks. Crinecerfont was excreted in the milk of rats with a milk-to-plasma ratio of 1.5 to 12.

19.1.2. Toxicokinetic Data

The TK data from pivotal toxicology studies are summarized under the respective toxicological study review in Section 19.1.7. TK results from pivotal 6-month rat and 12-month dog studies are presented in Table 97 and Table 98 below. In general, crinecerfont exposure increases with dose but in a less than dose-proportional manner following oral administration of crinecerfont free base both in rats and dogs. In rats, a 25-fold increase in dose resulted in less than a 4-fold increase in exposure, reaching saturation at doses ≥ 250 mg/kg/day. No significant accumulation was observed after repeated oral administration of crinecerfont free base in 6-month rat study. In dogs, a 10-fold increase in dose resulted in up to a 2-fold increase in exposure and approached saturation at doses ≥ 300 mg/kg/day. Accumulation of up to 2-fold was observed in the 12-month dog study.

Table 97. TK Parameters of 6-Month Repeated Toxicity Study in Rats

Sex	Dose (mg/kg/day)	C _{max} (ng/mL)			AUC ₂₄ (ng·h/mL)		
		Day 1	Day 28	Day 175	Day 1	Day 28	Day 175
Male	50	17600	21700	35000	257000	270000	327000
	250	26800	26800	44100	437000	390000	631000
	1250	35600	29000	49900	703000	366000	498000
Female	50	15800	19600	25100	222000	222000	358000
	250	48300	32900	43900	697000	458000	596000
	1250	38700	34900	47300	735000	416000	505000

Source: Applicant's Study Report SSR125543

Values are rounded to 3 significant figures.

Abbreviations: TK, toxicokinetic; AUC₂₄, area under the concentration-time curve from 0 to 24 h; C_{max}, maximum observed plasma concentration

Table 98. TK Parameters of 12-Month Repeated Toxicity Study in Dogs

Dose (mg/kg/day)	Day	Male		Female	
		C _{max} (ng/mL)	AUC ₂₄ (ng·h/mL)	C _{max} (ng/mL)	AUC ₂₄ (ng·h/mL)
100	1	16100	186000	21400	295000
	34	25900	300000	32600	444000
	91	29300	385000	48800	549000
	188	29300	338000	33600	355000
	363/370	43300	340000	51600	537000

Dose (mg/kg/day)	Day	Male		Female	
		C _{max} (ng/mL)	AUC ₂₄ (ng·h/mL)	C _{max} (ng/mL)	AUC ₂₄ (ng·h/mL)
300	1	16900	215000	30500	382000
	34	42200	526000	44100	569000
	91	46900	609000	47100	629000
	188	43100	441000	52900	715000
	363/370	46900	463000	48100	627000
1000	1	22000	279000	30300	375000
	34	39500	455000	57700	670000
	91	29600	395000	61400	842000
	188	34500	420000	60000	587000
	363/370	31100	399000	77200	804000

Source: Applicant's Study SSR125543

Abbreviations: AUC₂₄: area under plasma concentration versus time curve from 0 to 24 hours; C_{max}: maximum observed plasma concentration; TK, toxicokinetic

19.1.3. Primary Pharmacology

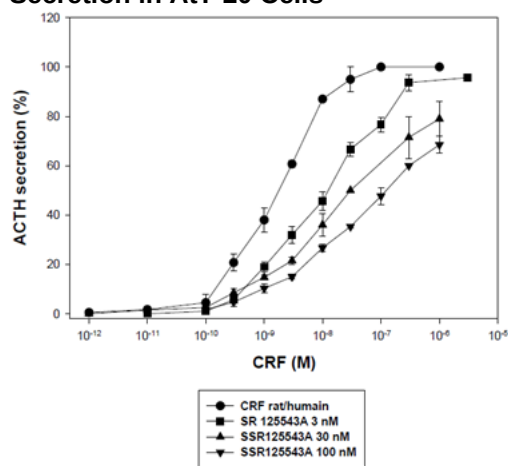
Crinecerfont is a selective antagonist of CRF1 receptors. Crinecerfont blocks the binding of CRF to CRF1 receptors in the pituitary but not to CRF2 receptors. Data from a series of in vitro and in vivo nonclinical pharmacology studies of crinecerfont were provided by the Applicant to demonstrate the pharmacological effects of crinecerfont. Primary pharmacological studies were conducted with crinecerfont HCl. These studies demonstrated that crinecerfont inhibits CRF1 receptors and antagonizes CRF-induced cyclic adenosine monophosphate (cAMP) synthesis and ACTH secretion from pituitary, and blocks stress-induced increases in ACTH in rats ([Table 99](#)). In the absence of stress or exogenous ACTH stimulation, crinecerfont had no effect on basal ACTH or adrenal hormones, suggesting low potential for adrenal insufficiency based on mechanism of action of crinecerfont. No signs of adrenal insufficiency were observed in pharmacology (or toxicology) studies in vivo.

Table 99. Reviewer's Primary Pharmacodynamic Studies

Test System	Key Findings/Relevance
In vitro binding assays using: • CHO and human Y79 cells expressing CRF1 receptors • Mouse, rat, and gerbil brain tissue • hCRF2a-CHO cells and hCRF-BP-CHO cells	Crinecerfont inhibited the ability of CRF to bind to CRF1 receptors, with IC₅₀ values of 0.6-3.99nM, but not hCRF2a or hCRF-BP receptors.
In vitro functional antagonist effects using: • cAMP synthesis induced by CRF in human Y79 retinoblastoma cells expressing CRF1 receptor • ACTH secretion induced by CRF in the AtT-20 mouse pituitary tumor cell line	In vitro functional tests showed that crinecerfont inhibited CRF-induced cAMP synthesis and ACTH secretion in cell cultures in a dose-dependent manner, confirming CRF1 receptor antagonist function of crinecerfont (Figure 30).

Test System	Key Findings/Relevance

Figure 30. Antagonism by Crinecerfont of CRF-Induced ACTH Secretion in AtT-20 Cells



Source: Study Report EVT0109)

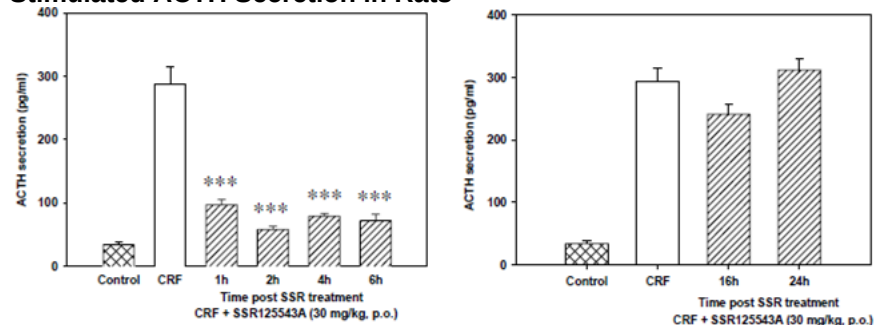
Abbreviations: ACTH, adrenocorticotropin hormone; CRF, corticotropin-releasing factor

In vivo binding and functional studies using:

- Evaluation of crinecerfont binding to CRF1 receptor in pituitary and brain
- Evaluation of crinecerfont effects on increased ACTH levels by CRF stimulation
- Evaluation of crinecerfont effects on increased ACTH levels by stress

- Crinecerfont bound to CRF1 receptors in pituitary and brain; with higher % occupancy of CRF1 receptors in pituitary than CRF1 receptors in brain at early timepoints (0.5-1h) and comparable occupancy at later timepoints (2-24h)
- Crinecerfont inhibited CRF-stimulated ACTH secretion significantly 1-6 hours postdose, and had no effects after 16 hours postdose ([Figure 31](#))

Figure 31. Time-Course Study of the Crinecerfont Effect on CRF-Stimulated ACTH Secretion in Rats



Source: Study Report EVV0033

***, p<0.001 versus CRF

Abbreviations: ACTH, adrenocorticotropin hormone; CRF, corticotropin-releasing factor; p.o., oral; SSR125543A, crinecerfont hydrochloride

Crinecerfont inhibited CRF-stimulated ACTH secretion significantly in a dose-dependent manner ([Figure 32](#)).

Test System	Key Findings/Relevance																								
	Figure 32. Dose-Response Study of the Crinecerfont Effect on CRF-Stimulated ACTH Secretion in Rats <table><caption>Approximate ACTH secretion (pg/ml) from Figure 32</caption><thead><tr><th>Treatment</th><th>ACTH secretion (pg/ml)</th><th>Significance</th></tr></thead><tbody><tr><td>0</td><td>~20</td><td></td></tr><tr><td>SSR</td><td>~20</td><td></td></tr><tr><td>CRF</td><td>~300</td><td></td></tr><tr><td>CRF + SSR125543A (1 mg/kg)</td><td>~340</td><td></td></tr><tr><td>CRF + SSR125543A (3 mg/kg)</td><td>~240</td><td></td></tr><tr><td>CRF + SSR125543A (10 mg/kg)</td><td>~100</td><td>***</td></tr><tr><td>CRF + SSR125543A (30 mg/kg)</td><td>~60</td><td>***</td></tr></tbody></table> Source: Study Report EVV0033 ***, $p < 0.001$ versus CRF **, $p < 0.01$ versus control Abbreviations: ACTH, adrenocorticotropin hormone; CRF, corticotropin-releasing factor; p.o., oral; SSR, 30 mg/kg crinecerfont hydrochloride; SSR125543A, crinecerfont hydrochloride Crinecerfont significantly ($p < 0.01$) antagonized stress-induced ACTH increase when administered PO at 10 mg/kg free base but not at 3 mg/kg free base. In nonstressed rats a daily PO dose of up to 1000 mg/kg crinecerfont free base had no effects on the level of basal ACTH, corticosterone, or prolactin compared to the vehicle control. PD studies showed that crinecerfont occupied CRF1 receptors in the pituitary and inhibited CRF-stimulation of ACTH secretion, and stress-induced increase ACTH levels. However, crinecerfont did not show effects on basal level of ACTH.	Treatment	ACTH secretion (pg/ml)	Significance	0	~20		SSR	~20		CRF	~300		CRF + SSR125543A (1 mg/kg)	~340		CRF + SSR125543A (3 mg/kg)	~240		CRF + SSR125543A (10 mg/kg)	~100	***	CRF + SSR125543A (30 mg/kg)	~60	***
Treatment	ACTH secretion (pg/ml)	Significance																							
0	~20																								
SSR	~20																								
CRF	~300																								
CRF + SSR125543A (1 mg/kg)	~340																								
CRF + SSR125543A (3 mg/kg)	~240																								
CRF + SSR125543A (10 mg/kg)	~100	***																							
CRF + SSR125543A (30 mg/kg)	~60	***																							

Source: Compiled by reviewer

Abbreviations: ACTH, adrenocorticotropin hormone; cAMP, cyclic adenosine monophosphate; CHO, Chinese hamster ovary; CRF, corticotropin-releasing factor; hCRF, human CRF; hCRF-BP, human CRF-binding protein; IC_{50} , half-maximal inhibitory concentration; PD, pharmacodynamic; PO, oral

19.1.4. Secondary Pharmacology

The off-target activity of crinecerfont was evaluated by in vitro binding and enzyme activity assays for 10 receptors and 12 enzymes, and by binding assays against more than 100 receptors, transporters, enzymes, and ion channels. Crinecerfont (10 μ M) inhibited acetylcholinesterase activity (88% inhibition), the sigma-1 receptor (54% inhibition), and the serotonin transporter (half-maximal inhibitory concentration [IC_{50}] of 3.0 μ M). Crinecerfont did not show any effect on contractility of isolated pig vas deferens up to 10 μ M, indicating lack of notable functional effects on the sigma-1 receptor. The potential off-target effects of crinecerfont on acetylcholinesterase and serotonin transporter were considered negligible when the micromolar affinity of crinecerfont to the nonspecific targets was compared with nanomolar affinity to CRF1 receptors. Therefore, clinically relevant off-target activities of crinecerfont were not identified.

19.1.5. Safety Pharmacology

Crinecerfont's effects on cardiovascular, autonomic nervous system, central nervous system (CNS), respiratory, renal, and gastrointestinal (GI) systems were assessed using in vitro and in vivo safety pharmacology studies ([Table 100](#)). Crinecerfont tosylate salt was used in safety pharmacology studies. No significant acute effects were observed on neurobehavioral function in rats, cardiovascular function in dogs, respiratory function in guinea pigs, renal function in rats, or gastrointestinal function in rats at clinically relevant doses. Crinecerfont showed no potential for clinical arrhythmia risk based on human ether-à-go-go-related gene (hERG) current (<5% inhibition) or isolated rabbit Purkinje fiber action potential assays at up to 10µM crinecerfont concentrations. Respiratory depression (increased inspiratory, expiratory, and relaxation times, accompanied by airway obstruction indicated by increased pause and enhanced pause) was observed in anesthetized guinea pigs at a 1000 mg/kg oral dose. No effects on respiratory parameters were observed at doses ≤100 mg/kg (0.2-fold maximum recommended human dose [MRHD]). Anesthetized guinea pigs may have been more sensitive to crinecerfont than other species, as all animals had tonal loss in hind paws under sedation. There were no significant effects of crinecerfont on the respiratory system in repeat-dose toxicity studies in mice, rats, and dogs, indicating the respiratory safety risk of crinecerfont is low. Overall, the safety pharmacology data supported crinecerfont clinical investigations and no remarkable acute safety concerns were identified at clinically relevant exposure levels.

Table 100. Safety Pharmacology Studies

System/Study	Key Findings/Relevance
Cardiovascular System hERG assay in CHO cell line and action potential assay in rabbit Purkinje fiber. Evaluation of potential cardiovascular effects in anesthetized dogs or conscious dogs	- No remarkable hERG inhibition (4.7% inhibition at 10µM) or effects on action potential were observed in vitro - No remarkable changes in ECG parameters up to 30 mg/kg in anesthetized dogs (~2-fold C_{max} MRHD) or conscious telemetered dogs up to 1000 mg/kg (~0.4-fold MRHD)
Central Nervous System Evaluation of potential effects on neurobehavioral, convulsion/seizure risk, sedative or wakeful, motor coordination and muscle tone, and locomotor and rearing activity were evaluated in studies conducted in mice or rats	No remarkable crinecerfont-related effects on: - Behavior or body temperature (2-fold MRHD C_{max}) - Pentylenetetrazole-induced convulsions and mortality (~2-fold MRHD C_{max}) - Latency to fall asleep or on sleeping time (~2-fold MRHD C_{max}) - Motor coordination or muscle tone (~7-fold MRHD C_{max}) - Exploratory behavior, psychostimulant or depressive effects (~7-fold MRHD C_{max})
Respiratory System Potential respiratory system effects in guinea pigs	At high dose of 1000 mg/kg, respiratory depression (increased inspiratory, expiratory, and relaxation times; with airway obstruction, indicated by increased pause and enhanced pause) was noted. No effects at doses ≤100 mg/kg (≤0.2-fold MRHD C _{max}). Respiratory-system-related adverse effects were not observed in repeat-dose toxicity studies in mice, rats, and dogs.

System/Study	Key Findings/Relevance
Renal System Potential renal and urinary system effects in male rats	Crinecerfont at 10 mg/kg had no effects on renal function (0.6-fold of MRHD C_{max}). Crinecerfont at doses ≥ 100 mg/kg (exposure >0.6 -fold MRHD) were associated with decreased creatinine clearance (20-39% at ≥ 100 mg/kg), increased blood creatinine (+13-29% at ≥ 100 mg/kg) and blood urea (+23-40% at ≥ 100 mg/kg) and urinary effects of decreased creatinine excretion (-30%), concentration and excretion of Na^+ (24 and 31%) and Cl^- (29 and 37%) and Na^+/K^+ ratio (30%). No changes in urine electrolyte or kidney histology were observed in repeat-dose toxicity studies.
Gastrointestinal System Potential GI/ulcerogenic effects in rats	No remarkable crinecerfont-related effects on GI transit, emptying or acid secretion up to 1000 mg/kg, or ulcers at doses up to 1230 mg/kg (10-fold MRHD C_{max})

Source: Compiled by reviewer

Exposure multiples are calculated using human PK values (C_{max} =5387 ng/mL); reported in Report 2023-PM-281.

Abbreviations: CHO, Chinese hamster ovary; C_{max} , maximum observed plasma concentration; ECG, electrocardiogram; GI, gastrointestinal; IC_{50} , concentration inhibiting 50% activity; MRHD, maximum recommended human dose; PK, pharmacokinetic

19.1.6. Pharmacodynamic Drug Interactions

No data were provided on nonclinical pharmacodynamic drug interactions.

19.1.7. Toxicology

19.1.7.1. General Toxicology

The toxicity of crinecerfont was evaluated in a series of single- and repeat-dose studies in mice, rats, and dogs. The target organs for crinecerfont were liver (mouse, rat, and dog), thyroid gland (rat and dog), and GI tract (mouse and rat). In early toxicology studies in rats with the tosylate salt, crinecerfont was associated with mortality due to hemorrhage and changes in coagulation parameters (increase in fibrinogen and prolonged prothrombin time [PT] and activated partial thromboplastin time [APTT]), in addition to the findings in liver, thyroid gland, and GI tract. The bleeding adverse effects were not observed in the pivotal nonclinical studies conducted with free-base crinecerfont, the form of crinecerfont proposed for the commercial drug product. The assessment of the pivotal chronic 6-month rat and 12-month dog studies are summarized in Sections [19.1.7.1.1](#) and [19.1.7.1.3](#), respectively.

19.1.7.1.1. 6-Month Oral Toxicity Study in Rats With a 6-Week Recovery Period, Study TXC1269

Key Findings

The 6-month rat study was conducted with a once-daily oral gavage dose of 0, 50, 250 or 1250 mg/kg crinecerfont free base. No crinecerfont-related mortality or clinical signs were observed. Crinecerfont was associated with partially reversible mild hematological changes (decreased red blood cell parameters and increased lymphocytes at ≥ 250 mg/kg/day, at exposure ≥ 7 -fold MRHD). Marked increases in PT (+52 to 60%) and APTT (+80 to 90%) were noted in

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males at ≥ 250 mg/kg/day (total exposure ≥ 7 -fold MRHD) without any signs of hemorrhage, which were likely associated with changes in liver function.

Crinecerfont was associated with partially reversible minimal to moderate liver lesions (centrilobular hypertrophy, vacuolation, multinucleated hepatocytes, hepatocyte anisokaryosis, and minimal hepatocyte necrosis) that correlated with liver enlargement and change in clinical chemistry (such as increased γ -glutamyl transferase, cholesterol, and decreased triglycerides) in all dose groups (≥ 50 mg/kg/day, 4-fold MRHD). The liver findings were mainly related to the induction of hepatic drug-metabolizing enzymes, which was consistent with the finding of the decrease in exposure following repeated dosing in rats.

Reversible minimal to mild thyroid follicular cell hyperplasia was observed in males at 1250 mg/kg/day (7-fold MRHD) and in females at ≥ 50 mg/kg/day (4-fold MRHD) with dose-related increase in incidence and severity, and may be secondary to liver enzyme induction ([Wu and Farrelly 2006](#)).

Crinecerfont was associated with forestomach lesions which included epithelial hyperplasia with hyperkeratosis, parakeratosis, and/or dyskeratosis to erosion, ulceration, and epithelial necrosis. The forestomach lesions were observed in all groups (≥ 50 mg/kg/day, 4-fold MRHD), and in the vehicle control group, with increasing incidence and severity with increasing dose of crinecerfont. One control female found dead on Day 116 had stomach perforations possibly related to the irritant action of the vehicle or to trauma. The lesion in rat forestomach was considered species-specific and may not be clinically relevant based on the absence of a nonglandular stomach in humans and the tolerability of the final clinical oral formulations.

Crinecerfont exposure saturation was observed in both sexes at doses ≥ 250 mg/kg. The NOAEL was not determined (≤ 50 mg/kg/day) for this study, and the exposure multiple for this study was ≤ 4 -fold at MRHD. In a complementary 6-month rat study, the NOAEL was 15 mg/kg/day with exposure comparable to the MRHD (see below, Section [19.1.7.1.2](#)).

Table 101. Methods of 6-Month Oral Toxicity Study in Rats

Study Feature	Method Details
Dose and frequency of dosing	0, 50, 250 or 1250 mg/kg/day, once daily for 26 weeks
Route of administration	Oral gavage
Formulation/vehicle	(b) (4)
Species/strain	Rat Sprague Dawley Crl:CD(SD)
Number/sex/group	15/sex/group; additional 6/sex 6-week drug-free recovery (vehicle control and high dose)
Age	7 weeks
Satellite groups/unique design	TK: 9 /sex/group
Deviation from study protocol affecting interpretation of results	None

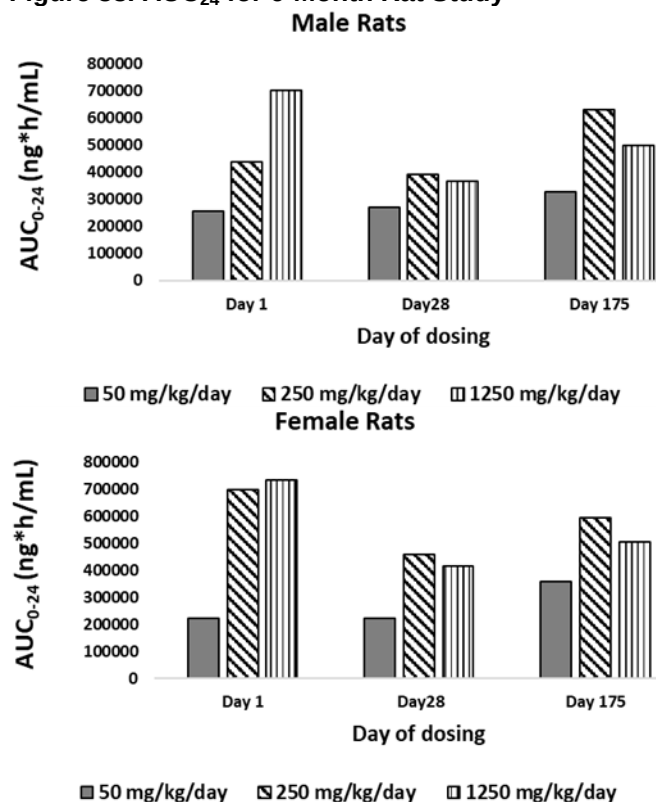
Source: Compiled by the reviewer

Abbreviations: TK, toxicokinetic; w/w, weight/weight

Table 102. Observations and Results of 6-Month Oral Toxicity Study in Rats

Parameter	Major Findings
TK	TK values for this study are shown in Table 97 (graphically presented in Figure 33). Exposures increased with dose but in a less than dose-proportional manner and reached/approached saturation at MD (250 mg/kg/day). No significant accumulation was observed after repeated oral administration of crinecerfont free base.

Figure 33. AUC₀₋₂₄ for 6-Month Rat Study



Source: Compiled by reviewer based on [Table 97](#)

Abbreviations: AUC, area under the concentration-time curve

Mortality	No crinecerfont-related death at any dose. Six animals (four controls, one in LD, one in HD) were found dead or sacrificed in morbid condition; four of six cases probably due to misdosing (acute lung lesions); one case (control)- kidney cancer and one case (control)- stomach perforation of undetermined cause.
Clinical signs	No treatment-related effects
Body weight and Food consumption	No treatment-related effects
Ophthalmology	No treatment-related effects. Observations in four females (one in LD, one in MD, and one in HD) were considered incidental.
Hematology	Crinecerfont caused mild decreases in red cell indices (Hb, HCT, MCH, MCV) and increased RBC distribution in both sexes and increased lymphocytes in males (+29% in MD, and up to +40% in HD). Hematological changes were partially reversible.
Coagulation	Crinecerfont caused an increased coagulation time (PT up to +60% and APTT up to +90%) in MD and HD males (partially reversible).

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Parameter	Major Findings
Clinical chemistry	Increased GGT values (up to 26% at ≥ 50 mg/kg/day) which correlated with liver hypertrophy. Minimal to mild increases in cholesterol (≥ 250 mg/kg/day), globulin (≥ 50 mg/kg/day), and glucose (1250 mg/kg/day) and decreases in triglycerides (≥ 250 mg/kg/day). Changes in clinical chemistry parameters were partially reversible.
Urinalysis	No treatment-related effects.
Organ weight	Increased liver weight up to +116% (≥ 50 mg/kg/day), which correlated with liver hypertrophy (partially reversible). Increased thyroid gland weight up to +57% (≥ 250 mg/kg/day), which persisted during recovery.
Macroscopic observations	Crinecerfont-related macroscopic findings were limited to mottled liver in one male at 1250 mg/kg/day, which correlated with mild increase in liver vacuolation. Observations not probably associated with crinecerfont: dark areas in the lungs of 3 rats probably associated with misdosing, and masses in kidney and subcutis microscopically correlated with tumors
Histopathology Adequate battery: Yes Peer reviewed: Yes	Liver Crinecerfont caused dose-related minimal to moderate centrilobular hypertrophy in both sexes (≥ 50 mg/kg/day), correlated with increased liver weight and possibly secondary to hepatic enzyme induction. Diffuse liver hypertrophy at 1250 mg/kg/dose; minimal to moderate multinucleated hepatocytes and minimal to mild anisokaryosis (≥ 250 mg/kg/day); increased vacuolation (≥ 50 mg/kg/day); minimal hepatocyte necrosis (≥ 250 mg/kg/day). Thyroid gland Crinecerfont-related minimal to mild thyroid gland follicular cell hyperplasia at 1250 mg/kg/day in males and ≥ 50 mg/kg/day in females with dose-related increase in incidence and severity (reversible); consistent with liver microsomal enzyme induction. Forestomach Lesions in the stomach (necrosis, ulcers, erosion, hyperplasia, hyperkeratosis/dyskeratosis, parakeratosis, edema, and mixed cell inflammatory infiltrate) were observed in both sexes in vehicle and treated groups with increasing trend in incidence with dose but not in severity. The lesion in rat forestomach was considered species-specific and not likely to be clinically relevant.
NOAEL	The NOAEL for the 6-month study in rat was ≤ 50 mg/kg/day. The C_{max} and AUC_{24} were $\leq 25,100$ ng/mL and 327,000 ng·hr/mL, respectively (safety margin ¹ of approximately 4-fold AUC at MRHD).

Source: Compiled by the reviewer

¹ Safety margin was calculated from $AUC = 88,802$ ng·hr/mg (Source: 2023-PM-281 Modeling Analysis Report).

Abbreviations: APTT, activated partial thromboplastin time; AUC_{24} , Area under plasma concentration versus time curve from 0 to 24 h; C_{max} , maximum observed plasma concentration; GGT, gamma-glutamyl transferase; Hb, hemoglobin; HCT, hematocrit; HD, high dose; LD, low dose; MCH, mean corpuscular hemoglobin; MCV, mean cellular volume; MD, mid dose; MRHD, maximum recommended human dose; NOAEL, no-observed-adverse-effect level; PT, prothrombin time; RBC, red blood cell; TK, toxicokinetic

19.1.7.1.2. Complementary 6-Month Oral Toxicity Study in Rats With a 6-Week Recovery Period, Study TXC1412

Key Findings

This study was conducted as a complementary study to the previous 6-month study (TXC1269) to determine the no-observed-effect level or no-observed-adverse-effect level (NOAEL) by using lower doses (NOAEL was not established in study TXC1269). In this study, no remarkable treatment-related mortality, clinical signs, change in body weight gain, food consumption or clinical pathology findings were observed. Microscopic findings were limited to reversible mild multinucleated hepatocytes and minimal anisokaryosis (1/15 female) and minimal centrilobular hepatocyte hypertrophy in males at 15 mg/kg/day. These liver findings were not considered adverse effects because of low incidence and minimum to mild severity. Mild to moderate ulceration, epithelial hyperplasia, submucosal edema and/or subacute inflammation of nonglandular stomach were observed in control and treated groups, which were associated with vehicle and incidence was exacerbated by crinecerfont.

The TK values for this study are shown in [Table 103](#). The systemic exposure increased in a dose-proportional manner in males and increased in a less than dose-proportional manner in females. The NOAEL for the study was 15 mg/kg/day. The maximum observed plasma concentration (C_{max}) and area under the concentration-time curve from 0 to 24 hours (AUC_{24}) values at the NOAEL on Day 178 were 18,000 ng/mL and 177,000 ng·hr/mL for males, and 11,300 ng/mL and 117,000 ng·hr/mL for females.

Table 103. TK Parameters of the 6-Month (Complementary) Rat Study

Sex	Dose (mg/kg/day)	C_{max} (ng/mL)			AUC_{24} (ng·hr/mL)		
		Day 1	Day 29	Day 178	Day 1	Day 29	Day 178
Male	5	3220	4900	5150	30900	48300	52500
	15	8270	9520	18000	74200	118000	177000
Female	5	2700	3770	7460	28500	29000	72200
	15	8940	8330	11300	64400	73600	117000

Source: Study Report TXC1412

Values are rounded to 3 significant figures

The exposure at the NOAEL was ~1-fold the MRHD, which was calculated from the AUC_{24} (117,000 ng·hr/mL) for females on Day 178 and human $AUC = 88,802$ ng·hr/mg (Source: 2023-PM-281 Modeling Analysis Report).

Abbreviations: AUC, area under the concentration-time curve; C_{max} , maximum observed plasma concentration; MRHD, maximum recommended human dose; NOAEL, no-observed-adverse-effect level; TK, toxicokinetic

Table 104. Methods of 6-Month Oral Toxicity Study in Rats With 6-Week Recovery Period

Study Feature	Method Details
Dose and frequency of dosing	0, 5 or 15 mg/kg/day, once daily for 26 weeks
Route of administration	Oral gavage
Formulation/vehicle	(b) (4)
Species/strain	Rat Sprague Dawley Crl:CD(SD)
Number/sex/group	15/sex/group; additional 6/sex 6-week drug-free recovery (vehicle control and high dose)
Age	7 weeks
Satellite groups/unique design	TK: 9 /sex/group (3 animals /sex in control group)
Deviation from study protocol affecting interpretation of results	None

Source: Compiled by the reviewer

Abbreviations: TK, toxicokinetic; w/w, weight/weight

19.1.7.1.3. 12-Month Oral Toxicity Study in Dogs With an 8-Week Recovery Period, Study TXC1204

Key Findings

The 12-month dog study was conducted with once-daily oral gavage doses of 100, 300 or 1000 mg/kg crinecerfont. Crinecerfont caused reversible minimal to moderate liver lesions (centrilobular hypertrophy, eosinophilic droplets, and pigmented hepatocytes) that correlated with liver enlargement and change in clinical chemistry (such as increased alkaline phosphatase and decreased albumin) at ≥ 100 mg/kg/day. Mild decreases in red cell parameters and increases in platelets were noted at ≥ 100 mg/kg/day. All the findings observed were not considered adverse effects based on their low magnitude, low incidence, reversibility, and/or lack of dose response. The NOAEL for this study was 1000 mg/kg/day. The AUC₂₄ values at the NOAEL were 399,000 ng·hr/mL for males and 804,000 ng·hr/mL for females. The safety margin based on exposure was ~4-fold, which was calculated using the AUC₂₄=399,000 ng·hr/mL (males) at NOAEL and human PK AUC₂₄=88,802 ng·hr/mg.⁹

Table 105. Methods of 12-Month Oral Toxicity Study in Dogs

Study Feature	Method Details
Dose and frequency of dosing	0, 100, 300 or 1000 mg/kg/day, once daily for 12 months
Route of administration	Oral gavage
Formulation/vehicle	(b) (4)
Species/strain	Beagle dog
Number/sex/group	4/sex/group; additional recovery animals 2/sex for group 1 (vehicle control) and group 4
Age	13-15 months
Deviation from study protocol affecting interpretation of results	None

Source: Compiled by the reviewer

Abbreviation: w/w, weight/weight

Table 106. Observations and Results of 12-Month Oral Toxicity Study in Dogs

Parameter	Major Findings

⁹ Source: 2023-PM-281 Modeling Analysis Report

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Parameter	Major Findings
TK	The plasma crinecerfont exposures increased less than dose-proportionally (Table 98). Crinecerfont accumulation of about 2-fold was noted after repeat dosing.
Mortality	No crinecerfont-related death was noted. Four animals (one each from control, LD, MD, and HD) were found dead, and one control animal was euthanized because of morbid condition, between Day 25 and 112 of the dosing period. The necropsy and histopathological findings observed in these 5 animals include red discoloration of lung, foamy light red content and/or debris in bronchi and trachea, and hemorrhage and edema in alveoli, which were attributed to misdosing/aspiration (gavage error or regurgitation) associated with the vehicle (b) (4). These findings were observed both in control and treatment groups and were unlikely related to crinecerfont.
Clinical signs	No crinecerfont-related clinical signs were observed. Clinical signs such emesis, abnormal feces, and excessive drooling (ptyalism) were observed in both control and treated groups. Skin lesions (swelling, redness and/or granules), which were microscopically associated with epidermal hyperplasia and folliculitis (probably due to colonies of <i>Malassezia</i> yeast present on skin surface) were observed in 2/4 LD females, 1/4 male and 1/4 female MD and 1/4 female HD.
Body weight	Statistically significant decreases in mean body weight in crinecerfont-treated groups (up to -10%) were observed. The changes were small in magnitude and not dose-responsive and were not considered adverse.
Food consumption	No remarkable crinecerfont-related changes in food consumption were noted.
Ophthalmology	Unremarkable
Electrocardiography	No crinecerfont-related abnormalities were noted.
Hematology	Crinecerfont caused mild decreases in red cell indices (Hb, HCT, MCH) in both sexes, and increased reticulocytes in males, and increases in platelets in both sexes (+59% in LD and MD, and up to +113% in HD, partially reversible).
Coagulation	Reversible minimal PT prolongation in 1 MD female (+34%) and 1 HD female (+38%) were not considered adverse.
Clinical chemistry	Reversible/partially reversible increase in ALP at all doses (mean 2- to 4-fold males, 2- to 6-fold females, up to 10-fold maximum individual animal change from pretest), increase in globulin at MD and HD (up to +85%) and decreased albumin at MD and HD (up to -46%), which were probably associated with liver hypertrophy and signs of metabolizing enzyme seen by histopathological examination.
Urinalysis	Unremarkable
Organ weights	Reversible increase in liver weights at MD and HD in males (up to +17%) and in all doses in females (up to +48%) were observed, which were correlated with centrilobular hepatocellular hypertrophy. Moderately decreased thymus weights were observed in males and females in all dose groups but were not dose-responsive and were not considered adverse.
Macroscopic observations	Thickened skin at the base of the ear pinna was observed in four females at all doses and one male at MD, which were associated microscopically with epidermal hyperplasia and folliculitis. Red mucosa and prominent vasculature at the surface were observed in one HD male.
Histopathology	Crinecerfont caused minimal to moderate centrilobular hepatocellular hypertrophy in both sexes at all doses (≥ 100 mg/kg/day), eosinophilic droplets at MD and HD (≥ 300 mg/kg/day), and pigmented hepatocytes at ≥ 100 mg/kg/day. All liver changes were reversible. These findings were considered adaptive change to the treatment (metabolizing enzyme induction), and not considered an adverse effect. Persistent minimal thymic lymphoid depletion was observed in all doses, which lacked a dose-response relationship. This finding was not considered adverse based on minimal severity. Urinary bladder urothelial polypoid hyperplasia with hemorrhage was observed in one HD male, which was considered incidental.

Parameter	Major Findings
NOAEL	The NOAEL for the 12-month study in dogs was 1000 mg/kg/day. The C _{max} and AUC ₂₄ at NOAEL were 31,100 ng/mL and 399,000 ng·hr/mL, respectively (5-fold MRHD).

Source: Compiled by the reviewer

Safety margin was calculated from AUC =88,802 ng·hr/mg (Source: 2023-PM-281 Modeling Analysis Report).

Abbreviations: ALP, alkaline phosphatase; AUC₂₄, area under plasma concentration versus time curve from 0 to 24 hours; C_{max}, maximum observed plasma concentration; HD, high dose; LD, low dose; MCH, mean corpuscular hemoglobin; MD, mid dose; MRHD, maximum recommended human dose; NOAEL, no-observed-adverse-effect level; PT, prothrombin time; TK, toxicokinetic; w/w, weight/weight

19.1.7.2. Genetic Toxicology

The Applicant evaluated the genotoxicity of crinecerfont (tosylate salt) by in vitro and in vivo assays. Crinecerfont tested negative for genotoxicity both in the in vitro and in vivo assays.

Table 107. Summary of Genetic Toxicology Study Findings

Study Title/Study No.	Key Findings
Bacterial reverse mutation test on <i>Salmonella typhimurium</i> (Ames test)/ HIS1394 GLP compliance: Yes Valid study: Yes	Negative for mutagenic potential in five <i>Salmonella typhimurium</i> strains (TA98, TA100, TA1535, TA102 and TA1537) at 50-2500 µg/plate concentration (±S9 metabolic activation).
In vitro gene mutation assay at the locus TK ⁺ in mouse lymphoma L5178Y cells/LYM0101 GLP compliance: Yes Valid study: Yes	Negative for mutagenic potential at concentration of 12.5-250 µg/mL (±S9 metabolic activation).
Micronucleus test – In vivo oral genotoxicity study in the rat/MUT0136 GLP compliance: Yes Valid study: Yes	Negative for mutagenic potential. No increase in micronucleated polychromatic erythrocytes in bone marrow at oral doses of 500-2000 mg/kg daily for 2 days (at exposure ~3-fold MRHD).

Source: Compiled by reviewer from studies HIS1394, LYM0101 and MUT0136.

Safety margin was calculated from C_{max} =5387 ng/mg (Source: 2023-PM-281 Modeling Analysis Report) and crinecerfont plasma concentration of 17498 ng/mL from micronucleus test (MUT0136).

Abbreviations: C_{max}, maximum observed plasma concentration; GLP, good laboratory practice; MRHD, maximum recommended human dose; TK, thymidine kinase

19.1.7.3. Carcinogenicity

The Applicant evaluated the oncogenic potential of crinecerfont by conducting 2-year rat and 6-month transgenic mouse carcinogenicity studies. Crinecerfont did not increase the incidence of tumors in Tg.rasH2 mice treated for 26 weeks at oral doses of 5, 50, 500 or 1500 mg/kg/day. In the 2-year rat study, crinecerfont increased the incidence of combined thyroid gland follicular cell adenoma and carcinoma in females at 100 mg/kg/day crinecerfont, the highest dose tested (4-fold MRHD). Crinecerfont did not increase the incidence of tumors in rats at 15 mg/kg/day, which is approximately 2 times the MRHD based on AUC. There were no statistically significant crinecerfont-related increases in the incidence of any other tumors. The thyroid gland follicular cell tumors were likely due to continuous stimulation of thyroid stimulating hormone (TSH) secondary to liver enzyme induction that causes increased clearance of thyroid hormones. This mechanism of inducing thyroid gland follicular cell hyperplasia and subsequent adenoma and carcinoma development is rodent-specific and is not considered relevant to humans ([Wu and Farrelly 2006](#); [Bartsch et al. 2018](#)).

19.1.7.3.1. A 104-Week Oral Oncogenicity Study in
Sprague Dawley Rats

Key Findings

The 2-year rat carcinogenicity study was conducted by administering once-daily oral gavage 0, 5, 15 or 100 mg/kg/day crinecerfont. The incidence of combined thyroid follicular cell adenomas and carcinomas increased significantly (in both trend and pairwise analyses) in female rats at the highest dose tested, 100 mg/kg/day (4-fold MRHD based on AUC). No evidence of increased tumorigenicity was seen in male rats up to approximately 4 times MRHD or in females rats up to approximately 2 times MRHD based on AUC.

Table 108. Methods of 104-Week Oral Oncogenicity Study in Rats

Study Feature	Method Details
Dose and frequency of dosing	0 (water), 0 (vehicle), 5, 15 or 100 mg/kg/day, once daily for 2 years
Route of administration	Oral gavage
Formulation/vehicle	(b) (4)
Species/strain	Rat/ CD1(ICR)
Number/sex/group	70/sex/group; TK: 6/sex/group (3 for controls)
Age	8 weeks
Deviation from study protocol affecting interpretation of results	None

Source: Compiled by reviewer.

Abbreviations: TK, toxicokinetic; w/w, weight/weight

Table 109. Observations and Results of 2-Year Oncogenicity Study in Rats

Parameters	Key Findings																																																																																														
TK	Table 110. TK Parameters of Crinecerfont in Rat Oncogenicity Study <table><tr><th>Study Day</th><th>NBI-74788 Dose (mg/kg)</th><th>Sex</th><th>AUC_{0-t} (ng·h/mL)</th><th>C_{max} (ng/mL)</th><th>T_{max} (h)</th><th>t_{1/2} (h)</th></tr><tr><td rowspan="6">1</td><td rowspan="2">5</td><td>Male</td><td>28600</td><td>2700</td><td>6.00</td><td>3.12</td></tr><tr><td>Female</td><td>24000</td><td>1800</td><td>8.00</td><td>-</td></tr><tr><td rowspan="2">15</td><td>Male</td><td>68400</td><td>5500</td><td>8.00</td><td>-</td></tr><tr><td>Female</td><td>66100</td><td>6480</td><td>6.00</td><td>6.52</td></tr><tr><td rowspan="2">100</td><td>Male</td><td>442000</td><td>33900</td><td>8.00</td><td>-</td></tr><tr><td>Female</td><td>332000</td><td>27900</td><td>6.00</td><td>11.1</td></tr><tr><td rowspan="6">182</td><td rowspan="2">5</td><td>Male</td><td>48000</td><td>4180</td><td>8.00</td><td>-</td></tr><tr><td>Female</td><td>54500</td><td>5580</td><td>6.00</td><td>6.50</td></tr><tr><td rowspan="2">15</td><td>Male</td><td>106000</td><td>8100</td><td>8.00</td><td>-</td></tr><tr><td>Female</td><td>246000</td><td>20000</td><td>8.00</td><td>-</td></tr><tr><td rowspan="2">100</td><td>Male</td><td>470000</td><td>38300</td><td>8.00</td><td>-</td></tr><tr><td>Female</td><td>438000</td><td>41600</td><td>6.00</td><td>5.17</td></tr><tr><td rowspan="3">688</td><td rowspan="2">5</td><td>Female</td><td>78400</td><td>6390</td><td>6.00</td><td>6.08</td></tr><tr><td>15</td><td>Female</td><td>180000</td><td>17100</td><td>6.00</td><td>8.28</td></tr><tr><td>100</td><td>Female</td><td>370000</td><td>34600</td><td>6.00</td><td>6.11</td></tr></table> Source: Study Report 882-098 (with slight re-arrangement) - = Not Calculated * T_{last} at 24 hours for each profile therefore AUC_{0-t} is equivalent to AUC₂₄ Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum observed plasma concentration, T_{max}, time to maximum observed plasma concentration, t_{1/2}, half-life; T_{last}, time of last sampling The increase in systemic exposure was dose-proportional over the dose range of 5 to 100 mg/kg/day on Day 1 and increased less than dose-proportionally with multiple doses (Day 182 in both sexes, and Day 688 in females [no data for males on Day 688]). The maximum systemic exposure was on Day 182. Accumulation was observed in low-dose females on Day 688; no accumulation was observed in mid and high doses. The difference in exposure with sex was minimal, except for mid dose on Day 182.	Study Day	NBI-74788 Dose (mg/kg)	Sex	AUC _{0-t} (ng·h/mL)	C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)	1	5	Male	28600	2700	6.00	3.12	Female	24000	1800	8.00	-	15	Male	68400	5500	8.00	-	Female	66100	6480	6.00	6.52	100	Male	442000	33900	8.00	-	Female	332000	27900	6.00	11.1	182	5	Male	48000	4180	8.00	-	Female	54500	5580	6.00	6.50	15	Male	106000	8100	8.00	-	Female	246000	20000	8.00	-	100	Male	470000	38300	8.00	-	Female	438000	41600	6.00	5.17	688	5	Female	78400	6390	6.00	6.08	15	Female	180000	17100	6.00	8.28	100	Female	370000	34600	6.00	6.11
Study Day	NBI-74788 Dose (mg/kg)	Sex	AUC _{0-t} (ng·h/mL)	C _{max} (ng/mL)	T _{max} (h)	t _{1/2} (h)																																																																																									
1	5	Male	28600	2700	6.00	3.12																																																																																									
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	15	Male	68400	5500	8.00	-																																																																																									
		Female	66100	6480	6.00	6.52																																																																																									
	100	Male	442000	33900	8.00	-																																																																																									
		Female	332000	27900	6.00	11.1																																																																																									
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		Female	54500	5580	6.00	6.50																																																																																									
	15	Male	106000	8100	8.00	-																																																																																									
		Female	246000	20000	8.00	-																																																																																									
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	100	Female	370000	34600	6.00	6.11																																																																																									
Mortality	There were no crinecerfont-related statistically significant differences in mortality between controls and test article groups. The survival rate of high-dose males trended lower after Week 52, but the difference was not statistically significant. The survival level (15 animals, 21.4% survival rate) in high-dose males triggered termination of the group at Week 87 as per the protocol. The remaining male treatment groups were terminated at Week 94 because the water control male survival was reduced to 20 animals. The female treatment groups were terminated at Week 101 when the water control group was reduced to 20 animals.																																																																																														
Body weight	Decreased body weight gains up to -13% and -17% at Week 84 in mid- and high-dose males, respectively, and decreased up to -11% in females ≥5 mg/kg/day compared to vehicle control. The changes were not consistently statistically significant and in females lacked dose dependence, therefore, the effects on body weight were not considered adverse effect.																																																																																														
Food consumption	Food consumption was reduced in vehicle and all crinecerfont treatment groups in both sexes compared to the water control group. Reduced food consumption was unlikely due to crinecerfont and was probably associated with the vehicle.																																																																																														

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Parameters	Key Findings
Neoplastic findings	Statistically significant (in trend and pairwise analyses) increase in the incidence of combined thyroid follicular cell adenomas and carcinomas was observed in females at 100 mg/kg/day compared to both water and vehicle control females. The incidence of benign thyroid follicular cell adenomas in 100 mg/kg/day females was 8/70 (11.4%) compared to 0/70 (0%) in water controls and 2/70 (2.9%) in vehicle controls, whereas the incidence of thyroid follicular cell carcinomas in 100 mg/kg/day females was 5/70 (7.1%) compared to 0/70 in both water and vehicle controls. The incidence of combined thyroid follicular cell tumors was 13/70 (18.6%). These findings were dose-dependent and exceeded the historical control ranges at the facility. The incidence of combined follicular cell adenoma and carcinoma was statistically significant both in trend ($p < 0.05$) and pairwise ($p < 0.01$) analysis and was likely associated with crinecerfont treatment. The incidence of thyroid follicular cell adenomas (7.1%) and carcinomas (2.9%) was increased in 100 mg/kg/day males compared to water and vehicle male controls. The incidence of thyroid follicular cell adenomas was higher than the historical control range of up to 5.1%, whereas the incidence of carcinomas was within the historical control range of up to 3.3%. These findings in males were not statistically significant.
Nonneoplastic findings	Crinecerfont was associated with increased incidences of chronic progressive nephropathy, bile duct hyperplasia (mild to moderate) and periportal vacuolation (mild to severe), and mild to moderate islet hemorrhage/pigment/inflammation/fibrosis.

Source: Compiled by reviewer based on Study Report 882-098

Safety margin was calculated from AUC = 88,802 ng·hr/mg (Source: 2023-PM-281 Modeling Analysis Report).

Abbreviations: AUC₂₄, Area under plasma concentration versus time curve from 0 to 24 hours; C_{max}, maximum observed plasma concentration; NOAEL, no-observed-adverse-effect level

19.1.7.3.2. A 26-Week Oral Oncogenicity Study in CByB6F1-Tg(HRAS)2Jic Mice

Key Findings

Crinecerfont did not increase the incidence of tumors in Tg.rasH2 mice treated for 26 weeks at oral doses of 5, 50, 500, or 1500 mg/kg/day. The positive control group treated with N-Nitroso-N-methylurea developed tumors, showing the study was conducted appropriately.

Table 111. Methods of 26-Week Oral Oncogenicity Study in Transgenic Mice

Study Feature	Method Details
Dose and frequency of dosing	0 (water), 0 (vehicle), 5, 50, 500 or 1500 mg/kg/day, once daily for 26 weeks; Single IP dose of 75 mg/kg/day N-Nitroso-N-methylurea (NMU) (positive control)
Route of administration	Oral gavage
Formulation/vehicle	(b) (4)
Species/strain	Mouse/ CB6F1-TgN (rasH2)
Number/sex/group	25 animals/sex/group; TK: 39 animals/sex/group (6 animals for controls); Positive control: 10 animals/sex
Age	8 weeks
Deviation from study protocol affecting interpretation of results	None

Source: Compiled by reviewer

Abbreviations: IP, intraperitoneal; NMU, N-Nitroso-N-methylurea; TK, toxicokinetic; w/w, weight/weight

Table 112. Observations and Results of 26-Week Oncogenicity Study in Transgenic Mice

Parameters	Key Findings					
Toxicokinetics	Table 113. Summary of Crinecerfont Plasma TK Parameters in Mouse Oncogenicity Study					
		Dose	C _{max} (ng/mL)		AUC ₂₄ (ng·h/mL)	
	Sex	(mg/kg/day)	Day 1	Day 182	Day 1	Day 182
	Male	15	3150	6720	29000	56500
		50	12800	16200	144000	125000
		500	23800	26600	430000	315000
		1500	56200	42200	782000	532000
	Female	15	3110	4290	41300	50800
		50	11400	12800	131000	103000
		500	40400	23000	638000	280000
		1500	45300	36000	742000	322000
	Source: Report 882-097					
	Values rounded to 3 significant figures					
	Abbreviations: AUC, area under the concentration-time curve; C _{max} , maximum observed plasma concentration; TK, toxicokinetic					
	The exposures of crinecerfont increased in a less than dose-proportional manner, and no accumulation was observed on Day 182. In contrast, plasma exposures were reduced on Day 182 compared to Day 1, indicating hepatic drug-metabolizing enzyme induction by crinecerfont. The C _{max} for HD on Day 182 was 42,200 ng/mL for males and 36,000 ng/mL for females. The AUC ₂₄ at HD on Day 182 was 532,000 ng·hr/mL for males and 322,000 ng·hr/mL for females.					
Mortality	No crinecerfont-related mortality was observed, and there were no significant differences in survival rates between controls and crinecerfont-administered groups.					
Clinical observations and mass findings	No crinecerfont-related remarkable clinical observations or palpable mass findings were observed. Higher incidence of nodules related to NMU were observed in the positive control group as compared to vehicle/water controls, as expected.					
Body weight	No remarkable differences in body weight and body weight change between controls and crinecerfont-treated groups in both sexes. An increase in body weight gain was observed in the NMU-treated (positive control) group compared with control groups and crinecerfont groups, consistent with increased food consumption. This finding in the positive control group was not toxicologically relevant and would not affect the validity of the study.					
Food consumption	No remarkable crinecerfont-related changes in food consumption were observed. The increase in mean food consumption values in both sexes in the positive control group compared with water and vehicle controls correlated with the increased body weight in the positive control group.					
Gross pathology	Crinecerfont-related gross findings were limited to liver diffuse tan discoloration (2 males at 500 mg/kg/day and 1 male and female at HD) that correlated with crinecerfont-related hepatocellular vacuolation. The incidence was low and was not considered toxicologically relevant.					
Organ weights	Crinecerfont-related dose-dependent increase in liver weight was observed in all dose levels in males (up to 80%) and at ≥50 mg/kg/day females (up to 54%). These changes correlated with hepatocellular vacuolation noted in males at all dose levels and females at ≥500 mg/kg.					

Parameters	Key Findings
Neoplastic findings	No crinecerfont-related oncogenic effects were observed at any dose in either sex based on trend ($p < 0.05$) and pairwise ($p < 0.01$) analyses. In the positive control group, statistically significant skin papilloma and stomach papilloma were observed, consistent with tumor findings in mice of this strain treated with NMU.
NOAEL	The NOAEL for oncogenic effect for 26-month Tg(HRAS)2Jic mice study was 1500 mg/kg/day crinecerfont.

Source: Compiled by reviewer based on Study Report 882-097

Abbreviations: AUC₂₄, area under plasma concentration versus time curve from 0 to 24 hours; C_{max}, maximum observed plasma concentration; HD, high dose; LD, low dose; MD, mid dose; NMU, N-nitroso-N-methylurea; NOAEL, no-observed-adverse-effect level

19.1.7.4. Reproductive Toxicology

19.1.7.4.1. Oral Male and Female Fertility Study in Rats

Key Findings

In a fertility study conducted by daily oral administration of crinecerfont tosylate to mature male and female rats at dose of 0, 150, 300 or 1000 mg/kg/day, no remarkable toxicities on fertility were observed in male and female rats up to the dose of 1000 mg/kg/day (2-fold MRHD based on AUC). However, crinecerfont tosylate was related with deaths or preterminal euthanasia in mid- and high-dose males, which were associated with hemorrhage and changes in coagulation parameters (prolongation of PT and APTT, and low platelet counts). The NOAEL for fertility in males and females was 1000 mg/kg/day which corresponded to exposures 2 times the MRHD. The NOAEL for paternal toxicity was the low dose (150 mg/kg/day).

Table 114. Method for Oral Male and Female Fertility Study in Rats

Study Feature	Method Details
Dose and frequency of dosing	0 (vehicle), 150, 300 or 1000 mg/kg/kg by oral gavage once daily Males were dosed for 28 days prior to cohabitation and up to 21 days during cohabitation Females were dosed 14 days prior to cohabitation and for up to 21 days during cohabitation and through Gestation Day 7
Route of administration	Oral gavage
Formulation/vehicle	0.6% methylcellulose aqueous solution
Species/strain	Sprague Dawley/ CrI:CD(R)(SD)IGS BR
Number/sex/group	24/sex/group
Age	9-10 weeks
Deviation from study protocol affecting interpretation of results	None

Source: Compiled by reviewer

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Table 115. Observations and Results of FEED Study in Rats

Parameters	Key Findings
Mortality	Seven males (4/24 in MD and 3/24 in HD) were found dead or euthanized early due to morbidity. The causes of death of 3 MD (3/24) and one HD (1/24) males were associated with prolongation of coagulation times (increased PT and APTT, lower platelet count and increased fibrinogen) and hemorrhages, (b) (4) Death in 1 HD male was due to arthropathy, likely accidental. The causes of death in 1 MD male and 1 HD male were not determined. In females, no crinecerfont-related deaths were observed.
Clinical observations	Chromodacryorrhea (reddish tear) and muzzle with red/brown material were observed at LD (1/20) and MD (2/20) males. Partial alopecia was observed at HD (1/20) in females.
Body weight	No remarkable effects on body weight or body weight gain in males and females.
Food consumption	No remarkable effects on food consumption in males. Slight decrease in food consumption in females at MD (-6%) and HD (-11%) during first week of the prehabitation period. Transient, slight decrease in food consumption (-6% to -9%) during gestation was observed in all doses. The change in food consumption was transient and small in magnitude and was not associated with change in body weight gain, and not considered adverse.
Hematology and coagulation	No remarkable effects on platelet counts in males at Day 56 (end of study). Minimal to mild prolongation of PT and/or APTT in males at all doses (up to +2.5-fold in PT and APTT), but the changes were not dose-responsive. Increased PT and APTT were associated with higher fibrinogen (+70%). The prolongation with PT and APTT correlated with deaths due to hemorrhage in MD and HD.
Macroscopic observations	No remarkable macroscopic findings in males or females. There was no crinecerfont-related change in uterine weight.
Mating performance and fertility	No remarkable effects on estrous cycle parameters, mating index, or fertility index. The mating, pregnancy and fertility indices were 100% for all groups.

Parameters	Key Findings
Pregnancy and embryo-fetus	Increased mean preimplantation loss of 11% and lower mean number of implantation sites of 15.3 per dam were observed at HD compared to controls (4.5% mean preimplantation loss and mean number of implantation sites of 16.9 per dam). These findings were reported to be within the historical range of the facility and were not considered toxicologically remarkable (the historical data for the facility were not provided, but the findings were within the range of published data from another facility: preimplantation loss 4.77-18.51% and implantation sites 12.7-16.2 per animal¹⁰). Lower number of live fetuses (14.5) per dam was observed at HD compared to 15.8 live fetuses per dam for control, which was associated with the higher preimplantation loss observed at this dose level. The difference is minor and not considered toxicologically remarkable.
NOAEL	Based on the crinecerfont-related adverse effects (mortality) in males at MD and HD, the paternal NOAEL for the FEED study was the LD (150 mg/kg/day). No adverse effects were observed in female reproductive performance in all doses tested, and the maternal NOAEL was 1000 mg/kg/day. The NOAEL for fertility and reproductive performance in males was 1000 mg/kg/day corresponding to AUC₂₄ of crinecerfont tosylate salt ~172,000 ng·hr/mL for male rats and 257,000 ng·hr/mL in female rats (based on Day 28 in the 1-month study at 500 mg/kg/day). The plasma exposure (AUC) at the NOAEL 1000 mg/kg/day was 2- to 4-fold MRHD.

Source: Compiled by reviewer from Study FER0352.
Safety margin was calculated from AUC =88,802 ng·hr/mg (Source: 2023-PM-281 Modeling Analysis Report).
Abbreviations: APTT, activated partial thromboplastin time; AUC₂₄, area under plasma concentration versus time curve from 0 to 24 hours; FEED, fertility and early embryonic development; HD, high dose (1000 mg/kg/day); LD, low dose (150 mg/kg/day); MD, mid dose (500 mg/kg/day); MRHD, maximum recommended human dose; NOAEL, no-observed-adverse-effect level; PT, prothrombin time

19.1.7.4.2. Oral Embryo-Fetal Development in Rat

Key Findings

An embryo-fetal development study was conducted with daily oral administration of crinecerfont tosylate to pregnant female rats during the period of organogenesis from gestation day (GD) 6 to 17 at 0, 150, 500 or 2000 mg/kg/day. No remarkable toxicological effects on maternal reproductive performance and fetal development were observed up to 2000 mg/kg/day except for a slight decrease in food consumption (up to -14%) in dams in treatment groups. The decrease in food consumption was not associated with decreased body weight gain and was not considered an adverse effect. The NOAEL for rat maternal and developmental toxicity was 2000 mg/kg/day (exposure 4-fold MRHD based on AUC). The plasma exposure of crinecerfont reached near saturation at the low dose of 150 mg/kg/day (AUC₂₄=296,000 ng·hr/mL), which was comparable to exposure at the NOAEL of 2000 mg/kg/day (AUC₂₄=328000 ng·hr/mL).

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(b) (4)

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Table 116. Method for Oral Embryo-Fetal Development in Rat

Study Feature	Method Details
Dose and frequency of dosing	150, 500 or 2000 mg/kg/day; GD6 to GD17
Route of administration	Oral (gavage) 10 mL/kg
Formulation/vehicle	0.6% methylcellulose in water for injection
Species/strain	Rat OFA CrI: OFA (SD)
Number/sex/group	Main study: 23/sex/group TK: 3/control group; 9/treated group
Age	11-12 weeks
Deviation from study protocol affecting interpretation of results	None

Source: Compiled by reviewer

Abbreviations: GD, gestation day; TK, toxicokinetic

Table 117. Observations and Results of EFD Study in Rats

Parameters	Findings
TK (GD17- 12th day of dosing)	No increase in plasma exposure of crinecerfont occurred between 150 and 2000 mg/kg/day doses. Crinecerfont was also detected in control groups at low levels (6-106 ng/mL), attributed to sample contamination during blood collection or plasma preparation.

Table 118. Toxicokinetics of EFD Study in Rats

Parameter	Dose (mg/kg/day)		
	150	500	2000
T _{max} (h)	2	6	2
C _{max} (ng/mL)	27956	27366	24396
AUC ₂₄ (ng·hr/mL)	296415	325462	328446
AUC/Dose	1976	651	164

Source: Study TER0383

Exposure saturation at low dose – The plasma exposure (AUC₂₄) at 150 mg/kg/day and 2000 mg/kg/day (NOAEL) were 296,000 ng·hr/mL and 328,000 ng·hr/mL, respectively.

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum observed plasma concentration; EFD, embryo-fetal development; T_{max}, time to maximum observed plasma concentration

Mortality	None
Clinical signs, and body weight gain	Unremarkable
Food consumption	Slightly lower mean food consumption (~ -10%) in treated groups.
Pregnancy status (GD21), macroscopic examination of dams (GD21), gravid uterus weight (GD21), and pregnancy parameters	Unremarkable – no crinecerfont-related effects on pregnancy parameters

Parameters	Findings
Fetal examination	Treatment-related increased visceral variations (dilated renal pelvis and dilated uterus). The incidences of these visceral variations were slightly higher than historical ranges. Treatment-related slight increase in the incidence of fetal and litter skeletal malformations: misaligned sternebrae 3, 4 and 5 and shortened ribs (uni- or bilateral) were observed. The incidences of these defects were within or close to historical ranges and were not considered treatment-related adverse effects. Treatment-related slightly higher fetal and litter incidences of skeletal variations were observed. The incidences of these defects were within or close to historical ranges and were not considered treatment-related adverse effects.
NOAEL	Maternal and embryo-fetal developmental toxicity was 2000 mg/kg/day (the highest dose tested). The plasma exposure at the NOAEL was $AUC_{24}=328,000$ ng·hr/mL, which corresponds to ~4-fold MRHD.

Source: Compiled by the reviewer

Exposure margin was calculated from $AUC = 88,802$ ng·hr/mg (Source: 2023-PM-281 Modeling Analysis Report) at MRHD and AUC at NOAEL.

Abbreviations: AUC_{24} , Area under plasma concentration versus time curve from 0 to 24 hours; C_{max} , maximum observed plasma concentration; EFD, embryo-fetal development; GD, gestation day; MRHD, maximum recommended human dose; NOAEL, no-observed-adverse-effect level; T_{max} , postdose time to reach C_{max}

19.1.7.4.3. Embryo-Fetal Development Study in the Rabbit (TER0384)

Key Findings

An embryo-fetal development study was conducted with daily oral administration of crinecerfont tosylate to pregnant female rabbits during the period of organogenesis from GD6 to GD19 at 0, 100, 500, or 1000 mg/kg/day. The plasma exposures of crinecerfont were not dose-dependent between 100 mg/kg/day (low dose) and 1000 mg/kg/day (high dose), with approximately 2-fold exposure variation across doses, and similar mean systemic exposures were observed in the low and high dose groups. Crinecerfont was associated with slightly lower maternal body weight gain in all treatment groups compared to controls, corresponding with a slight reduction in mean fetal body weight in the high dose group (37.5 g versus 40.4 g in control group). There were a few fetuses that exhibited external, visceral, and/or skeletal skull malformations. The skull malformations included microcephaly, microstomia, acephalostomia, misshapen cerebrum and/or cerebellum, among others (details shown in [Table 123](#)).

There were four fetuses (all females) exhibiting one or more of these malformations, three in the 100 mg/kg/day group and one in the 1000 mg/kg/day group (total incidence of 0.8% fetuses and 7% litters across all dose groups combined). The observed malformations are rare and occurred at incidences above the historical range reported by the conducting laboratory. The observed malformations did not correlate with maternal toxicity. The NOAEL for fetal toxicity was not determined due to the increase in incidence of craniofacial malformations. The potential clinical relevance of the observed fetal malformations is discussed in Section [13](#) and the fetal craniofacial defects will be described in the labeling.

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Table 119. Methods for Embryo-Fetal Development Study in the Rabbit

Study Feature	Method Details
Dose and frequency of dosing	100, 500 or 1000 mg/kg/day; GD6 to GD19
Route of administration	Oral (gavage) 5 mL/kg
Formulation/vehicle	0.6% methylcellulose in water
Species/strain	New Zealand white rabbit
Number/sex/group	Main study: 25/group TK: 3/group; 6 control animals for coagulation study
Age	16-18 weeks
Deviation from study protocol affecting interpretation of results	None

Source: Compiled by reviewer

Abbreviations: GD, gestation day; TK, toxicokinetic

Table 120. Observations and Results of EFD Study in Rabbits

Parameters	Key Findings																			
Toxicokinetic	<table><tr><th colspan="4">Table 121. GD19 TK Parameters of Crinecerfont in EFD Study in Rabbits</th></tr><tr><th rowspan="2">Parameter</th><th colspan="3">Dose (mg/kg/day)</th></tr><tr><th>100</th><th>500</th><th>1000</th></tr><tr><td>C_{max} (ng/mL)</td><td>8470</td><td>15300</td><td>8690</td></tr><tr><td>AUC₂₄ (ng·h/mL)</td><td>138000</td><td>260000</td><td>139000</td></tr></table> Source: Report TER0384 Values rounded to 3 significant figures Abbreviations: AUC, area under the plasma concentration versus time curve from 0 to 24 hours; C_{max}, maximum observed plasma concentration; EFD, embryo-fetal development; GD, gestation day; TK, toxicokinetic The mean exposures at 100 and 1000 mg/kg/day were similar, indicating exposure saturation. Exposure increased ~2-fold for the 5-fold increase in dose to the mid dose, whereas between 500 and 1000 mg/kg/day, exposure decreased by ~2-fold for a dose increase by 2-fold. The exposures at 1000 mg/kg/day dose were highly variable.	Table 121. GD19 TK Parameters of Crinecerfont in EFD Study in Rabbits				Parameter	Dose (mg/kg/day)			100	500	1000	C _{max} (ng/mL)	8470	15300	8690	AUC ₂₄ (ng·h/mL)	138000	260000	139000
Table 121. GD19 TK Parameters of Crinecerfont in EFD Study in Rabbits																				
Parameter	Dose (mg/kg/day)																			
	100	500	1000																	
C _{max} (ng/mL)	8470	15300	8690																	
AUC ₂₄ (ng·h/mL)	138000	260000	139000																	
Mortality	No treatment-related mortality																			
Clinical signs	Unremarkable																			
Body weight	Slightly lower mean body weight gain (~20%) in treated groups compared to controls during treatment period (GD6-GD20), mainly due to changes at the beginning of the treatment																			
Food consumption	Lower mean food consumption (~20%) in the treated group during GD6-GD20 compared to the controls, correlated with the lower body weight gains																			
Pregnancy	No treatment-related effects on fertility and gestation indices																			
Coagulation	No crinecerfont-tosylate-related effects on PT and APTT were observed. (b) (4)																			
Macroscopic and microscopic examination of the dams	No remarkable treatment-related macroscopic and microscopic findings in dams were observed.																			
Gravid uterus weight	Slightly lower gravid uterus weight (-5% to -6% reduction) was observed.																			
Pregnancy parameters	Treatment-related lower fetal body weight at 1000 mg/kg/day (37.5 g vs. 40.4 g for controls), and increase in number of fetuses with lower weight were observed, as shown in Table 122 :																			
	<table><tr><th colspan="2">Table 122. Incidence and Litter Distribution of Fetuses of Low Weight</th></tr><tr><th>Parameter</th><th>Dose (mg/kg/day)</th></tr></table>	Table 122. Incidence and Litter Distribution of Fetuses of Low Weight		Parameter	Dose (mg/kg/day)															
Table 122. Incidence and Litter Distribution of Fetuses of Low Weight																				
Parameter	Dose (mg/kg/day)																			

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Parameters	Key Findings			
	0	100	500	1000
Number of evaluated pregnant females	20	19	20	20
20 g ≤ fetal weight < 25 g	0	3 (3 litters)	3 (3 litters)	7 (3 litters)
25 g ≤ fetal weight < 30 g	8 (5 litters)	13 (7 litters)	19 (7 litters)	25 (11 litters)
Total: fetal incidence	8/182 4% (5 litters)	16/166 10% (7 litters)	22/176 13% (7 litters)	32/182 17% (11 litters)

Source: Study Report TER0384

Fetal examination Slight retardation in ossification, a variation, was noted in all treatment doses and correlated with lower fetal body weights (<30 g).

Additional individual malformations in treated animals which were within the historical control range and/or considered incidental and unrelated to drug included: one female fetus with fluid-filled abdomen (1/176) and one female fetus with cerebral hemorrhage (1/176) at 500 mg/kg/day; one female fetus with absence of left kidney and ureter (1/183) at 1000 mg/kg/day. One very small female fetus (~50% the mean fetal body weight) at 1000 mg/kg/day had small ventricular chamber and malpositioned abdominal organs visceraally (1/183), with additional external and skeletal craniofacial malformations observed (described further below).

Multiple malformations (polymalformations), including craniofacial defects, were observed externally in 4 total female fetuses (3/166 fetuses from 3 litters at 100 mg/kg/day and 1/183 fetus at 1000 mg/kg/day). The defects included microcephaly with small eye bulges or malpositioned eyes, fused frontal bones, short snout, and absence of most of the head parts (acephalostomia). Additional visceral and skeletal craniofacial malformations were observed in the same fetuses, including hemorrhagic cerebrum, misshapen cerebellum, misshapen cerebrum, and small, fused skeletal regions. The Applicant summarized the observed malformations in the following table:

Table 123. Observed Malformations in EFD Study in Rabbits

Table 129. Observed Malformations in EP D Study in Rabbits				
Female	Fetal Weight (g)	Malformations		
		External	Visceral	Skeletal
100 mg/kg/day				
2F22 – fetus 3 Mated male 344518*	35.5	Microcephaly Small eyes bulge, bilateral	Hemorrhagic cerebrum Misshapen cerebellum	
2F31 – fetus 6 Mated male 344518*	41.6	Microcephaly Malpositioned eyes, bilateral	Misshapen cerebrum Absence of interhemispheric fissure Dilated cerebral ventricles (severe)	Nasal: small, fused Palatine: small, fused Frontal: small, fused
2F41 – fetus 3	37.0	Microstomia Short snout Small eyes bulge, left Short tail	Misshapen cerebrum Absence of interhemispheric fissure Dilated cerebral ventricles (severe)	Nasal and frontal: fused Maxilla: small Fontanel: enlarged Caudal vertebral malformation
500 mg/kg/day				
3F55 – fetus 1	43.5		Hemorrhagic cerebrum, half of right hemisphere (internal)	
1000 mg/kg/day				

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Parameters	Key Findings
4F65 – fetus 11	20.7 Acephalostomia Gastroschisis Ectrodactyly Small ventricular chamber, thick septum Almost all abdominal organs malpositioned Nasal, frontal, parietal, intraparietal, zygomatic: absent Mandible: small Absence of phalanx

Source: Study Report TER0384

* Male mated with 4 other females of the study (2 controls, 1 at 100, 1 at 500 mg/kg/day) without fetal abnormalities.

Abbreviations: EFD, embryo-fetal development

The craniofacial malformations described are rarely observed in NZ white rabbit based on the conducting laboratory's historical control data. While the craniofacial malformations were only observed in female fetuses, any relationship to sex is unclear. The Applicant concluded that the observed malformations were not related to crinecerfont treatment because of the low incidence and the absence of a dose-related increase in malformations. However, given the apparent exposure saturation and the absence of dose-related increases in plasma drug exposure, we concluded that malformation incidence should not be delineated between different dose groups. To assess the overall incidence rate of craniofacial malformations, we combined all the crinecerfont-treated animals in the study to compare to concurrent and historical control incidence. The overall incidence of craniofacial malformations was 4 fetuses (4/525, 0.8%) from 4 different litters (4/59, 7%). We included the 1000 mg/kg/day fetus with polymalformations in our grouped analysis, but it was likely a unique case because it was significantly smaller than other fetuses (~50% lower body weight than the study mean) and had a different spectrum of malformations than the three 100 mg/kg/day fetuses with craniofacial malformations. Compared to malformations previously observed in the conducting lab, the craniofacial malformations in this crinecerfont study were different. Historical control data from the conducting laboratory included a single craniofacial malformation of anencephaly (1/1098, 0.09% incidence across 11 studies, ranging 0-0.6% in individual studies). Therefore, it was unclear whether crinecerfont was associated with the low incidence of malformations observed in this study. The malformation finding will be described in the labeling.

NOAEL No dose-specific NOAEL could be established because crinecerfont exposure was saturated across the dose range (C_{max} = 8470-15,200 ng/mL, AUC_{24} = 138,000-260,000 ng·hr/mL). There was no maternal toxicity identified in the study, up to approximately 3-times the MRHD exposure.

Potential crinecerfont-related effects on embryo-fetal development observed in the study at 2 to 3 times MRHD exposures included slightly lower mean fetal body weight and a low incidence of craniofacial malformations.

Source: Compiled by the reviewer

Exposure margin was calculated from $AUC = 88,802$ ng·hr/mL (Source: 2023-PM-281 Modeling Analysis Report) at MRHD and AUC at NOAEL

Abbreviations: APTT, activated partial thromboplastin time; AUC_{24} , Area under plasma concentration versus time curve from 0 to 24 hours; C_{max} , maximum observed plasma concentration; EFD, embryo-fetal development; GD, gestation day; MRHD, maximum recommended human dose; NOAEL, no-observed-adverse-effect level; NZ, New Zealand; PT, prothrombin time

19.1.7.4.4. Pre- and Postnatal Development Study in Rats

Key Findings

A pre- and postnatal development study was conducted with daily oral administration of crinecerfont free base to pregnant rats during the period of organogenesis to weaning from GD7 to lactation day 20 at 0, 15, 150 or 250 mg/kg/day. Crinecerfont was not associated with remarkable toxicity on reproductive performance or development up to a dose of 250 mg/kg/day (at 4-fold MRHD based on AUC).

Table 124. Methods for Pre- and Postnatal Development Toxicity Study in Rats

Study Feature	Method Details
Dose and frequency of dosing	15, 150 or 250 mg/kg/day; GD7 to LD20
Route of administration	Oral (gavage) 5 mL/kg
Formulation/vehicle	(b) (4)
Species/strain	Sprague-Dawley (CrI:CD[SD])
Number/sex/group	F ₀ Main Study: 22 females/group F ₁ : 22/sex/group TK: 6/group; 3 vehicle control
Age	66-76 days
Deviation from study protocol affecting interpretation of results	None

Source: Compiled by reviewer

Abbreviations: GD, gestation day; LD, lactation day; TK, toxicokinetic; w/w, weight/weight

Table 125. Observations and Results of PPND Study in Rats

Parameters	Key Findings																												
Toxicokinetic/ lactation exposure	<table><tr><th colspan="4">Table 126. Summary TK Parameters of Crinecerfont on LD14</th></tr><tr><th>Generation</th><th>Dose (mg/kg/day)</th><th>C_{max} (ng/mL)</th><th>AUC₂₄ (ng·h/mL)</th></tr><tr><td rowspan="3">F₀</td><td>15</td><td>8270</td><td>48200</td></tr><tr><td>50</td><td>13800</td><td>142000</td></tr><tr><td>250</td><td>28500</td><td>392000</td></tr><tr><td rowspan="3">F₁ (combined sexes)</td><td>15</td><td>731</td><td>5000</td></tr><tr><td>50</td><td>1530</td><td>9940</td></tr><tr><td>250</td><td>4400</td><td>21500</td></tr></table> Source: Report 20156519 Values rounded to 3 significant figures Abbreviations: AUC_{0-last}, area under the plasma concentration versus time curve from 0 hours to last quantifiable concentration; C_{max}, maximum observed plasma concentration; LD, lactation day; TK, toxicokinetic The systemic exposures of crinecerfont and M6 metabolite exhibited an increase in a less than dose-proportional manner over the dosing range of 15 to 250 mg/kg. The levels of M6 were 2 to 19% of the parent crinecerfont systemic exposure independent of the treatment group and generation. On LD14, milk samples were analyzed for crinecerfont and M6. The levels in milk at 4 hours/8 hours postdose were 14,000/23,300 ng/mL (low dose), 20,500/46,400 ng/mL (MD), and 51,300/56,200 ng/mL (HD). The concentration of crinecerfont in milk increased with increasing doses and was 1.5 to 12 times greater when compared to concentrations in plasma, showing that the pups were exposed to crinecerfont via milk.	Table 126. Summary TK Parameters of Crinecerfont on LD14				Generation	Dose (mg/kg/day)	C _{max} (ng/mL)	AUC ₂₄ (ng·h/mL)	F ₀	15	8270	48200	50	13800	142000	250	28500	392000	F ₁ (combined sexes)	15	731	5000	50	1530	9940	250	4400	21500
Table 126. Summary TK Parameters of Crinecerfont on LD14																													
Generation	Dose (mg/kg/day)	C _{max} (ng/mL)	AUC ₂₄ (ng·h/mL)																										
F ₀	15	8270	48200																										
	50	13800	142000																										
	250	28500	392000																										
F ₁ (combined sexes)	15	731	5000																										
	50	1530	9940																										
	250	4400	21500																										
F ₀ mortality	There was no crinecerfont-related mortality.																												

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Parameters	Key Findings
Clinical observations	No crinecerfont-related clinical findings were observed in dams (F ₀ females) during gestation or lactation.
Body weight	Mean body weight gain increased significantly in all crinecerfont dose groups for overall gestation period of GD7 to GD20 by up to 22% compared to the controls. The changes were transient. Maternal mean body weight gain increased significantly in all crinecerfont dose groups during the entire lactation period (LD1 to LD20) by up to 71% from the controls; unlikely to be toxicologically relevant.
Food consumption	No crinecerfont-related change in maternal food consumption during gestation and lactation
F ₀ parturition data	No crinecerfont treatment effects on parturition parameters were observed.
F ₀ maternal necropsy observations	No crinecerfont-related abnormalities were observed at maternal necropsy examination.
F ₁ litter observation	No remarkable differences between crinecerfont-treated and control groups in any litter parameters (total pups delivered, liveborn, stillborn, viability index, and sex ratio)
F ₁ pups clinical and necropsy observation	There was an increased incidence of an enlarged eye, which occurred in 12 pups (4.9%) from 7 different litters (7/21, 33%) in the HD group. These findings in the eyes were not considered toxicologically relevant because only 3 pups (2/21 litters, 10%) had related histopathology findings at necropsy.
Postweaning F₁ generation	
Mortality	No treatment-related deaths were occurred.
Body weight	No significant effects on the mean body weight or mean body weight gains in the F ₁ males or females during the premating or gestation intervals at any dose level were observed.
Sexual maturation	There were no crinecerfont-related effects on sexual maturation parameters of F ₁ males or females. Mean age of sexual maturation (day of preputial separation for males and vaginal opening for females and mean body weight at sexual maturation) were not affected by crinecerfont exposure in the placenta and through milk. Sexual maturation was achieved in 43.5 to 44.8 days for males and 29.8 to 30.7 days for females.
Behavioral assessments F₁ generation	
Memory and Learning	No crinecerfont-related effects on learning and memory by the Passive Avoidance test on PND 24, and by Morris Water Maze in PND65-90 in either sex at any dose level
Estrous cycle, mating, and fertility	No treatment-related effects were observed on estrous cyclicity, mating and fertility in F ₁ generation rats
Macroscopic examinations	No crinecerfont-related macroscopic findings were observed in F ₁ males and females. Enlarged and dark red discoloration of right eye was observed in one 250 mg/kg/day male and one 250 mg/kg/day female, which was related to anterior segment hemorrhage.
Histopathology	No crinecerfont-related microscopic findings were observed in F ₁ pups. Eye lesions characterized by mild lens degeneration, uveal and retinal atrophy, and hypertrophy/hyperplasia of cornea, and immature iridocorneal angle were observed in one male and one female at high dose, but not considered adverse because of the low incidence rate.

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Parameters	Key Findings
NOAEL	Crinecerfont exhibited no adverse effects on development or reproductive performance in the PPND study in rats at doses up to 250 mg/kg/day. The maternal and fetal NOAEL was 250 mg/kg/day with AUC _{last} of 392,000 ng·hr/mL on LD14, which represents approximately 4-fold MRHD based on AUC.

Source: Compiled by the reviewer

¹ Safety margin was calculated from AUC =88,802 ng·hr/mg (Source: 2023-PM-281 Modeling Analysis Report) at MRHD and AUC at NOAEL.

Abbreviations: AUC₂₄, area under plasma concentration versus time curve from 0 to 24 hours; C_{max}, maximum observed plasma concentration; GD, gestation day; HD, high dose; LD, lactation day; MD, mid dose; MRHD, maximum recommended human dose; NOAEL, no-observed-adverse-effect level; PND, postnatal day; PPND, pre- and postnatal development; TK, toxicokinetic

19.1.7.4.5. Juvenile Toxicity Study in Rats on Postnatal Day 21 Through 49

Key Findings

In a juvenile rat study conducted with oral daily administration of crinecerfont free base on postnatal day (PND) 21 to PND49 at 0, 15, 100 or 1000 mg/kg/day, the toxicological findings in juvenile rats were largely comparable to the findings observed in adult rats (liver and thyroid gland toxicity, and changes in coagulation parameters). Increased liver weight associated with hypertrophy in females (partially reversed), and increased thyroid/parathyroid weight associated with thyroid follicular cell hypertrophy, minimal to moderate increase in coagulation times and decreased triglycerides in males (nonreversible) were observed at ≥ 100 mg/kg/day. Hepatocellular hypertrophy in liver and follicular cell hypertrophy of thyroid gland were possibly related to enzyme induction and were also seen in adult rats. Slightly delayed sexual maturation in 1000 mg/kg/day males was noted. In females mated with untreated males after a 7-week recovery period, a higher mean number of pre- and postimplantation losses at 1000 mg/kg/day was observed. Crinecerfont was not associated with CNS effects. The NOAEL was the mid dose of 100 mg/kg/day, with exposure of ~2-fold MRHD based on AUC.

Table 127. Method for Oral Juvenile (PND21 to PND71) Toxicity Study in Rats

Study Feature	Method Details
Dose and frequency of dosing	15, 100 or 1000 mg/kg/day; PND21 to PND49
Route of administration	Oral (gavage) 5 mL/kg
Formulation/vehicle	(b) (4)
Species/strain	Sprague-Dawley (CrI:CD[SD])
Number/sex/group	Main study: 10/group/sex Recovery phase: 20/group/sex TK: 24/group; 6 vehicle control/sex
Age	PND21
Deviation from study protocol affecting interpretation of results	None

Source: Compiled by reviewer

Abbreviations: PND, postnatal day; TK, toxicokinetic; w/w, weight/weight

Table 128. Observations and Results of Juvenile (PND21 to PND70) Study in Rats

Parameter	Key Findings							
Toxicokinetics (end of dosing PND71; end of recovery PND119 (GD20))	Table 129. Summary of TK Parameters in Juvenile Study in Rats							
			Dose (mg/kg/day)					
			15		100		1000	
	Parameter	Sex	PND21	PND70	PND21	PND70	PND21	PND70
	C_{max} (ng/mL)	M	10200	9990	64500	21600	82500	26900
	F	11800	12200	80800	29400	104000	32800	
AUC_{24} (ng·h/mL)	M	108000	105000	747000	195000	941000	245000	
	F	103000	78100	857000	240000	110000	387000	
Source: 2.6.6 Toxicology Written Summary								
Values rounded to 3 significant figures								
Abbreviations: AUC_{0-last} , area under the plasma concentration versus time curve from 0 hours to last quantifiable concentration; C_{max} , maximum observed plasma concentration; PND, postnatal day; TK, toxicokinetic								
	Exposures of crinecerfont and metabolite NBI-756179 increased dose-proportionally from 15 to 100 mg/kg/day but very little increase occurred from 100 to 1000 mg/kg/day indicating exposure approximating saturation. Females showed slightly higher exposure than males. Decrease in crinecerfont exposure was observed from PND21 (Day 1) to PND70 (Day 49), likely due to autoinduction of metabolism.							
Mortality	No treatment-related mortality was observed. A total of 19 animals died across all groups: 4 in vehicle control, 4 in LD, 6 in MD, and 4 in HD. 15/19 deaths were due to gavage errors, potentially related to inadvertent aspiration of the vehicle (b) (4) this effect is not relevant in humans due to different clinical formulation and mode of oral administration (capsule). Two of the 19 deaths were unrelated to treatment while the cause of the death for 2/19 could not be determined.							
Clinical signs	Respiratory distress in all groups, likely attributed to aspiration of vehicle with irritant effects. Enlarged eyeballs (with dark eyeball and/ or protrusion of the conjunctiva) in 3 HD males							
Body weight	Unremarkable							
Food consumption	Sporadic decreases in food consumption were noted in treatment groups; Decreased food consumption (-13 to -19%) in HD males and females in Week 1.							
Ophthalmoscopy	Unremarkable							
Hematology	Decreased red cell mass: RBC count (-10%), Hb (-16%) and HCT (-16%) in males at all doses and in females at HD was noted. These changes were reversed at the end of recovery period.							
Clinical chemistry	Increased albumin (+8 to +25%), globulin (+11 to +32%), and cholesterol (+51 to 111%) levels in females at ≥100 mg/kg; decrease in glucose (-28%) and ALP (-24%) in HD males; decreased ALP (-32 to -43%) at all doses in females; decreased triglyceride (-52% to -74%), sodium (-5%), and chloride (-4%) in males at ≥100 mg/kg. All the changes in blood chemistry were reversible except decreased triglycerides in males at ≥100 mg/kg. The changes in blood chemistry were consistent with liver effects.							
Coagulation	Increased PT (+13%) and APTT (58%) in males at HD (reversible) was noted.							
Urinalysis	Unremarkable							
Sexual maturation	Slightly delayed balano-preputial separation in HD males (47.6 vs. 43.7 days in controls). No effect on vaginal opening was noted.							

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CRENESSITY (crinecerfont) oral capsule and oral solution

Parameter	Key Findings
Reproductive performance	No treatment-related effects on estrous cycling and fertility parameters (mating, mating and fertility indices, or conception rate) were observed in treated females. Increased preimplantation loss and decreased number of implants, and decreased live fetuses were observed in HD females mated with untreated males. Increased early resorptions and associated higher post implantation loss were noted in HD females. Decreased live fetuses was observed in HD females, which was associated with pre- and postimplantation loss
Hormone analysis (FSH, LH, corticosterone, prolactin, progesterone, and estradiol)	Minimal decreases were noted in prolactin and corticosterone levels in HD females at the end of recovery, which lacked pathology correlation.
CNS/ Neurobehavioral assessment (FOB, motor activity evaluation and Morris water maze tests)	No treatment-related effects on neurobehavioral parameters were observed.
Bone evaluation (femur length)	No treatment-related effect on femur length was noted at the end of the treatment or recovery
Gross pathology and organ weigh	Liver enlargement and/or mottled discoloration was observed in females at ≥ 100 mg/kg/day. Increased liver weight was observed in HD males and in females ≥ 100 mg/kg/day, which was correlated with liver enlargement and hepatocellular hypertrophy (partial recovery in females) Increased thyroid/parathyroid gland weight was observed in HD females, which was correlated with thyroid follicular cell hypertrophy.
Histopathology	Minimal hepatocellular hypertrophy was noted in HD males (2/10) and minimal to moderate hypertrophy with minimal to mild vacuolation in females at ≥ 100 mg/kg/day (9/10 at MD and HD); Liver weight increase, and hypertrophy were likely secondary to hepatic enzyme induction as observed from decreased exposure on Day 49 vs. Day 1. Minimal thyroid gland follicular cell hypertrophy was observed in HD males and in females at ≥ 100 mg/kg/day, consistent with increased thyroid/parathyroid gland weight. Respiratory tract microscopic changes of inflammation, degeneration, regeneration, and metaplasia were observed in both control and HD groups, probably due to aspiration and irritation from the vehicle.
NOAEL	The NOAEL for this juvenile toxicity study was 100 mg/kg/day (2-fold MRHD, by AUC) based on the significant and/or irreversible findings at 1000 mg/kg/day including fewer implants and higher number of early resorptions in females, decreased triglyceride in males and increased liver weight in females.

Source: Compiled by the reviewer

¹Safety margin was calculated from AUC =88,802 ng·hr/mg (Source: 2023-PM-281 Modeling Analysis Report) at MRHD and AUC at NOAEL.

Abbreviations: ALP, alkaline phosphatase; APTT, activated partial thromboplastin time; AUC, Area under plasma concentration versus time curve; CNS, central nervous system; FOB, functional observational battery; FSH, follicle-stimulating hormone; GD, gestation day; Hb, hemoglobin; HCT, hematocrit; HD, high dose; LD, low dose; LH, luteinizing hormone; MD, mid dose; MRHD, maximum recommended human dose; NOAEL, no-observed-adverse-effect level; PND, postnatal day; PT, prothrombin time; RBC, red blood cell

19.1.7.4.6. Juvenile Toxicity Study in Rats on PND4
Through PND21, With Developmental Observations
From PND22 Through PND70

Key Findings

For this study, juvenile rats were administered crinecerfont orally once daily at 0, 15, 100, 300 or 1000 mg/kg/day on PND4 to PND21 followed by a treatment-free period PND22 to PND70 before euthanasia on PND71. The recovery phase animals were euthanized on PND119 to PND121 (males) or GD21 (females).

The juvenile rats did not tolerate 1000 mg/kg/day dose (13-fold MRHD based on AUC), which resulted in early termination of the dose group. Crinecerfont-related findings in decedent animals included hepatocellular necrosis and vacuolation, increased hepatocellular mitosis, and thyroid gland follicular cell hypertrophy.

Crinecerfont was associated with significant decreases in body weight gain (up to -30%) and absolute body weights in all doses (≤ 0.5 -fold MRHD based AUC) during dosing (PND4 to PND21) and during the treatment-free period (PND22 to PND70), but these resolved after PND70. Sexual maturation parameters in both sexes were not affected by decrements in body weights (delayed growth). The decrease in learning and memory on PND24 (shortly after weaning) in 300 mg/kg/day males and females (at exposure 3-fold MRHD based on AUC) and the decrease in femur length in 300 mg/kg/day females on PND71 were considered related to low body weight gains (delayed growth), which were resolved during recovery period PND71 to PND121.

Decreases in lymphocytes and total white blood cell count at 300 mg/kg/day (at exposure 3-fold MRHD based on AUC) were observed on PND71, which were resolved at the end of recovery period. Increases in triglycerides were noted in 300 mg/kg/day males at the end of recovery period.

Crinecerfont was associated with thyroid gland follicular cell hypertrophy at all doses. This finding was not resolved at the end of the recovery period in 300 mg/kg/day males and all doses in females.

The reproductive and developmental NOAEL was 300 mg/kg/day with exposure approximately 4-fold the MRHD.

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CRENESSITY (crinecerfont) oral capsule and oral solution

Table 130. Method for Oral Juvenile (PND4 to PND21) Toxicity Study in Rats

Study Feature	Method Details
Dose and frequency of dosing	15, 100 or 1000 ^a /300 ^b mg/kg/day; PND4 to PND21
Route of administration	Oral (gavage) 7.5 mL/kg
Formulation/vehicle	(b) (4)
Species/strain	Sprague-Dawley (CrI:CD[SD])
Number/sex/group	Main study: 9-11/group/sex Recovery phase: 20/group/sex TK: 39-45/group; 9 vehicle control/sex
Age	PND4
Deviation from study protocol affecting interpretation of results	None

Source: Compiled by reviewer

^a Due to excess toxicity, animals at 1000 mg/kg/day were found dead or euthanized on PND33

^b A study extension was conducted and included a new high dose group (300 mg/kg/day)

Abbreviations: PND, postnatal day; TK, toxicokinetic; w/w/w, weight/weight/weight

Table 131. Observations and Results of Juvenile (PND4 to PND21) Study in Rats

Parameters	Key Findings				
Toxicokinetic	Table 132. Summary of TK Parameters for Crinecerfont in Juvenile Study in Rats				
Dose (mg/kg/day)	Sex	Postnatal Day 4		Postnatal Day 21	
		C _{max} (ng/mL)	AUC ₂₄ (ng·h/mL)	C _{max} (ng/mL)	AUC ₂₄ (ng·h/mL)
15	Male	10200	105000	6350	44300
	Female	6750	105000	5740	52400
100	Male	32100	158000	33300	204000
	Female	27800	133000	29900	246000
300	Male	48000	753000	61000	444000
	Female	48100	788000	39400	386000
1000	Male	83200	1170000	NP	NP
	Female	83100	1320000	NP	NP

Source: Toxicology Written Summary, Module 2.6.6

Values rounded to 3 significant figures

Abbreviations: AUC, area under the plasma concentration versus time curve; C_{max}, maximum observed plasma concentration; NP, not performed; TK, toxicokinetic

The plasma exposures (C_{max} and AUC_{0-t}) of crinecerfont increased in a less than dose-proportional manner from 15 to 300/1000 mg/kg/day. A 20-fold increase in dose from 15 to 300 mg/kg led to an increase in about 8-fold C_{max} and AUC_{0-t}. The exposures for 1000 mg/kg were for a single dose on PND4. T_{max} and T_{last} were 4-6 and 24 hours postdose, respectively. Exposures were comparable between males and females, with no accumulation after multiple doses. Exposures for 15 and 300 mg/kg/day doses trended low after multiple doses.

All metabolites (NBI-756179, NBI-742939 (M4), NBI-1084059 (M9) and 1084060 (M11)) increased in less than dose-proportional manner. Plasma levels of metabolites were <1% for M11, <5% for NBI-756179, <8% for M9, and <14% for M4. M11 accumulation was noted in all doses in both sex at PND21. The other metabolite accumulations were noted at 100 mg/kg/day dose in both sexes.

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Parameters	Key Findings
Mortality	Treatment-related mortalities occurred at 1000 mg/kg/day, which led to early termination of this dose group and the addition of another high-dose group at 300 mg/kg/day. There were 3, 2, 4, and 14 mortalities in males and 2, 2, 5 and 15 mortalities in females in 0, 15, 100, and 1000 mg/kg/day dose groups. Liver findings (hepatocellular necrosis, vacuolation, and increased mitosis) and thyroid gland follicular cell hypertrophy were observed in early decedent animals. Gavage-related findings were observed in some animals at 1000 mg/kg/day. The cause of death or clinical decline for some animals were not determined. There was no increase in treatment-related mortalities at ≤ 300 mg/kg/day dose groups.
Clinical signs	Treatment-related clinical signs (discolored black or purple abdominal skin) were observed in 15 and 100 mg/kg/day dose groups but not in the extended study at 300 mg/kg/day. The association of these clinical signs with crinecerfont was unclear.
Body weights	Treatment-related decrease in body weight gains and absolute body weights (delayed growth) were observed in all treatment groups during dosing period (PND4 to PND21) in both sexes (up to -31%), and beyond the dosing period (PND22 to PND70) and resolved or increased compared to the controls after PND70. Delayed growth did not affect sexual maturation but affected learning and memory (by passive avoidance assessments) on PND24 in both sexes and reduced femur length on PND70 in females at 300 mg/kg/day. Effects on learning and memory and femur length were reversed during later intervals.
Food consumption	No significant treatment-related effects were noted.
Sexual maturation	No treatment-related effects on sexual maturation. Delayed preputial separation in 15 mg/kg/day males and early vaginal potency in 15 and 300 mg/kg/day females were noted. These effects were not dose-dependent and were within historical control ranges for the facility and were not considered adverse effects.
Passive avoidance	No treatment-related effects on learning and memory at 15 and 100 mg/kg/day. Learning and memory were affected at 300 mg/kg/day on PND24 but resolved in later intervals (PNDs 31, 101, and 108).
Functional observation battery	No remarkable treatment-related effects: between PNDs 50 and 54, mean body temperatures (at 15 and 100 mg/kg/day) and hindlimb strength (100 mg/kg/day females) were lower compared to controls. The changes in body temperature were not dose-dependent, and the lower hindlimb strength was likely due to delayed growth rate. These findings were not observed at the later assessment intervals (between PNDs 97 and 101), consistent with completion of juvenile growth and development.
Motor activity (ambulation, fine movement), and	Decreased ambulation at 15 mg/kg/day (PND57 to PND69) and increased ambulation at 300 mg/kg/day (PND99 to PND103), but the toxicological significance was unclear as it was not dose-dependent and /or occurred long after off-drug period.
Morris water maze	No remarkable findings.
Estrous cycling, mating, and fertility	No remarkable effects on estrous cyclicity, mating and fertility.
Ovarian and uterine examinations and litter observations, and fetal external examinations	No remarkable findings.
Femur measurements	Slight decrease in femur length in females at 300 mg/kg/day on PND71 but not at later period (GD21/PND121).
Hematology	Decreased WBCs and lymphocytes at 300 mg/kg/day on PND71, resolved at end of recovery period (PND121/GD21).
Coagulation	Unremarkable

Parameters	Key Findings
Clinical chemistry	Increases in triglycerides in 300 mg/kg/day males at the end of the recovery period. The toxicological relevance of this finding after recovery period was not clear.
Gross pathology	No treatment-related gross findings on PND71 or at the end of recovery period (PNDs 119 to 121 or GD21).
Organ weight	Increased thyroid gland weight in both sexes at 15 and 100 mg/kg/day doses but not at 300 mg/kg/day. Increased thyroid gland weight correlated microscopically with follicular cell hypertrophy. Increased thyroid gland weight was not noted at the end of recovery period.
Histopathology	Minimal to mild thyroid gland follicular cell hypertrophy was observed at 15- and 100-mg/kg/day doses in males and females, and at 300 mg/kg/day in males on PND71. Thyroid gland follicular cell hypertrophy persisted during the recovery period in 300-mg/kg/day males (PNDs 119 to 121), and in all doses in females (GD21). Treatment-related hepatocellular necrosis or vacuolation were observed in early death animals at 1000 mg/kg/day (this dose was not tolerated and was terminated early). At PND71 to PND121 and GD21, low incidences of these liver toxicity findings were observed in all doses and control groups and were not considered treatment-related.
NOAEL	The developmental and reproductive NOAEL was the high dose (300 mg/kg/day, 4-fold MRHD based on AUC). The delayed growth (low body weights) at all doses and slightly decreased femur length at high dose in females and decreased total white blood cell count and lymphocytes were resolved at the end of the recovery period and were not considered permanent adverse effects on juvenile animals. Thyroid gland follicular cell hypertrophy and increased triglycerides were observed at the end of the recovery period. In absence of associated clinical conditions, these effects were not considered adverse.

Source: Compiled by reviewer

¹ Safety margin was calculated from AUC =88,802 ng·hr/mg (Source: 2023-PM-281 Modeling Analysis Report) at MRHD and AUC at NOAEL.

Abbreviations: AUC, Area under plasma concentration versus time curve; C_{max}, maximum observed plasma concentration; GD, gestation day; MRHD, maximum recommended human dose; NOAEL, no-observed-adverse-effect level; PND, postnatal day; T_{last}, time of last measured plasma concentration; T_{max}, time to maximum plasma concentration; WBC, white blood cell

19.1.7.4.7. Other Toxicology Studies

Comments on Inactive Ingredients

Crinecerfont is presented in two oral dosage forms: soft gel capsules of 25 mg, 50 mg, and 100 mg (NDA 218808); and 50 mg/mL oral solution (NDA 218820). The two proposed clinical oral dosage formulations contain different excipients. [Table 133](#) and [Table 134](#) show the components and quantities of the crinecerfont 100 mg soft gel capsule and the 50 mg/mL oral solution, respectively. All the excipients, except for the propylene glycol (PG) dicaprylocaprate in soft gel capsules and the orange flavor in 50 mg/mL oral solution, are present in the FDA IID for oral formulations, and thus are not a safety concern. The safety of the two excipients (PG dicaprylocaprate and orange flavor) that are not in the IID database is assessed below.

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CRENESSITY (crinecerfont) oral capsule and oral solution

Table 133. Composition of Crinecerfont 100 mg Soft Gel Capsules

Material	% w/w	Quantity (mg/unit)	Function	Reference to Standards
Crinecerfont	(b) (4)	100.0 ¹	Drug substance	Module 3.2.S.4.1
Medium-chain triglycerides ²	(b) (4)	(b) (4)	(b) (4)	USP/NF, Ph. Eur.
Propylene glycol dicaprylate/dicaprate ⁴	(b) (4)	(b) (4)	(b) (4)	USP/NF, Ph. Eur.
Lauroyl polyoxyl-32 glycerides ⁵	(b) (4)	(b) (4)	(b) (4)	USP/NF, Ph. Eur.
Vitamin E polyethylene glycol succinate (Vitamin E TPGS)	(b) (4)	(b) (4)	(b) (4)	NF
Fill solution weight	100.0%	(b) (4)		
Soft gelatin capsule, gold ⁶	DMF	(b) (4)	Capsule shell	Pharmaceutical ⁷
Ink, black: (b) (4)	N/A ⁸		Ink	Pharmaceutical ⁷

Source: NDA 218808 Module 3.2.P.1

¹ The actual dispensed amount of crinecerfont drug substance (b) (4)

² Named Triglycerides Medium Chain in the Ph. Eur.

³ The actual dispensed amount of medium-chain triglycerides (b) (4)

⁴ Named Propylene Glycol Dicaprylocaprate in the Ph. Eur.

⁵ Named Lauroyl Macrogol, 32 Glycerides in the Ph. Eur.

⁶ Gelatin capsule shell contains Gelatin (NF), Sorbitol Special®/Glycerin Blend (USP), Titanium Dioxide (USP), Red Iron Oxide (NF, JP), Yellow Iron Oxide (NF, JP), Glycerin (USP), (b) (4)

⁷ As provided by the vendor.

⁸ Minimal quantity used for logo printing purposes only.

Abbreviations: DMF, Drug Master File; JP, Japanese Pharmacopoeia; Ph. Eur, European Pharmacopoeia; USP/NF, U.S.

Pharmacopoeia/National Formulary; w/w, weight/weight; N/A, not applicable

Table 134. Composition of Crinecerfont 50 mg/mL Oral Solution

Material	% w/w	Quantity (mg/mL)	Function	Reference to Standards
Crinecerfont	(b) (4)	50.0 ¹	Drug substance	Module 3.2.S.4.1 in NDA 218808
Medium-chain triglycerides	(b) (4)	(b) (4)	(b) (4)	Ph. Eur, USP/NF
Butylated hydroxytoluene	(b) (4)	(b) (4)	(b) (4)	Ph. Eur, USP/NF
Saccharin	(b) (4)	(b) (4)	(b) (4)	Ph. Eur, USP/NF
Orange flavor	(b) (4)	(b) (4)	(b) (4)	US FDA/EU Food Grade ⁴
Total solution weight	100.0%	(b) (4)		

Source: NDA 218820 Module 3.2.P.1

¹ Dispensed amount of crinecerfont (b) (4)

² Dispensed amount of medium-chain triglycerides (b) (4)

³ Orange flavor (b) (4)

⁴ As provided by the vendor.

Abbreviations: (b) (4) Ph. Eur, European Pharmacopoeia; US FDA, U.S. Food and Drug Administration; USP/NF, U.S. Pharmacopoeia/National Formulary; w/w, weight/weight

NDA 218808—Propylene Glycol Dicaprylocaprate (b) (4)

Propylene glycol dicaprylocaprate is used in the manufacturing of crinecerfont soft gel capsules (NDA 218808). The levels of PG dicaprylocaprate in 25 mg, 50 mg, and 100 mg soft gel capsule drug products are (b) (4) mg, (b) (4) mg, and (b) (4) mg, respectively. The maximum daily intake of PG dicaprylocaprate in the maximum 400-mg oral human dose (in patients concomitantly using a strong CYP3A4 inducer) is approximately (b) (4) mg. The Applicant used publicly available data and data from the manufacturer of the excipient to support its safe use.

The Applicant provided publicly available data from GLP-compliant oral acute, subchronic (90-day), and embryo-fetal developmental toxicity studies of PG dicaprylocaprate (Table 135). These studies demonstrated that there were no remarkable PG-dicaprylocaprate-related adverse effects. The maximum tolerated dose for acute toxicity study was >2000 mg/kg/day. The NOAEL for the 90-day rat study was the maximum dose tested (1000 mg/kg/day). No maternal or fetal toxicities were observed in a rat embryo-fetal developmental toxicity study up to 1000 mg/kg/day (the highest dose tested). In addition, safety assessment data generated by a read-across approach for PG esters with similar structure, properties, and functions were used to support the safety of PG dicaprylocaprate. The findings from read-across assessment of PG esters were negative for genotoxicity both in an in vitro and in an in vivo genotoxicity assay and did not show adverse effects on development or reproductive performance in rats (Table 136).

Table 135. Propylene Glycol Dicaprylocaprate GLP-Compliant Safety Assessments Summary

Study Type	Study Duration	Study Findings
Acute oral toxicity in rats	Single-dose, 14-day postdose observation	LD ₅₀ >2000 mg/kg; no occurrences of mortality, clinical signs of toxicity, or abnormal body weight gain were observed during the study
Oral toxicity study in rats	90 days, 34-day recovery	NOAEL ≥1000 mg/kg/day; no adverse effects were observed for clinical signs, mortality, body weight, feed consumption, water consumption, ophthalmoscopic examination, hematology, clinical chemistry, gross pathology, organ weights, and histopathology.
Embryo-fetal development toxicity study in rats	Oral gavage administration on GDs 6 to 15, sacrifice and necropsy on GD20	NOAEL >1000 mg/kg/day; no differences in implantations, number of live or dead fetuses, sex ratio, fetus body weights, number of litters, or fetus malformations between the treatment and control groups

Source: ECHA website for Decanoic acid, mixed diesters with octanoic acid and propylene glycol (EC number 271-516-3); <https://echa.europa.eu/registration-dossier/-/registered-dossier/15872/7/1>

Abbreviations: GD, gestation day; GLP, good laboratory practice; LD₅₀, lethal dose for 50% of test sample; NOAEL, no-observed-adverse-effect level

Table 136. Read-Across Summary of Propylene Glycol Esters Safety Assessments

Study Type	Study Duration	Study Findings
In vitro mammalian chromosomal aberration assay (Chinese hamster lung fibroblasts)	Not applicable	Test material: diester of 1,3-butandiol with C8/C10-fatty acids Concentrations of 10, 40, 60, 80, and 100 µg/mL were negative for the induction of structural and numerical chromosomal aberrations in the presence and absence of exogenous metabolic activation system.
In vivo micronucleus assay	Not applicable	Test material: fatty acid C18 and C18 unsaturated, epoxidized, Ester with ethylene glycol Single, oral dose at 5000 mg/kg was negative for the induction of micronuclei in polychromatic erythrocyte cells in mouse bone marrow.
Fertility and early embryonic development study in rats	Up to 18 weeks for mating, pregnancy, and lactation	Test material: not specified NOAEL =1000 mg/kg for P0, F1, and F2 generations; no adverse effect on general toxicity, reproductive performance, or maturation.

Source: ECHA website for Decanoic acid, mixed diesters with octanoic acid and propylene glycol (EC number 271051603); <https://echa.europa.eu/registration-dossier/-/registered-dossier/15872/7/1>

Abbreviations: NOAEL, no-observed-adverse-effect level

PG esters also have been used as food additives and nutraceutical products/dietary supplements. The mono- and diesters of propylene glycol are permitted as direct and secondary food additives [21 CFR 172.856, 21 CFR 173.340]. The estimated human acceptable daily intake of PG esters of fatty acids (determined by the Joint FAO/WHO Expert Committee on Food Additives) is 25 mg/kg/day in terms of PG ([Joint FAO/WHO Expert Committee on Food Additives 1974](#)), equivalent to ~80 mg/kg/day PG esters ([EFSA Panel on Food Additives and Flavourings et al. 2018](#)).

Since the maximum daily dose of PG dicaprylocaprate in the drug product (b) (4) mg, (b) (4) mg/kg/day) is lower than human recommended limit of 25 mg/kg/day in food additives and no adverse effects were observed in toxicological studies (NOAEL of 1000 mg/kg/day in rats, equivalent to multiple ~10-fold human exposure), the amount of PG dicaprylocaprate in crinecerfont soft gel capsule is not a safety concern for the target patient population of ≥4 years of age.

NDA 218820—Orange Flavor

Orange Flavor is a noncompendial excipient used in the manufacturing of crinecerfont oral solution 50 mg/mL drug product (NDA 218820). The maximum daily intake of orange flavor is (b) (4) mg in a 400-mg dose of crinecerfont. (b) (4)

The levels of (b) (4) in crinecerfont oral solution are within the levels in the IID. The (b) (4) is not listed in the IID, but it is generally recognized as safe under 21 CFR 182 (common food ingredients) by the drug master file holder. Considering (b) (4) as a common food ingredient, the maximum daily intake of (b) (4) mg orange flavor (b) (4) in crinecerfont drug product is not a safety concern.

Toxicological Risk Assessment of Impurities

The Applicant assessed the safety of the crinecerfont process intermediates, impurities, and degradants (b) (4)

(b) (4) using in silico evaluation for potential genotoxic structural alerts, skin and eye irritation assay, local lymph node assay, and in vitro genotoxicity assays. (b) (4)

The impurity (b) (4) is an organic impurity produced as a byproduct of the crinecerfont drug substance manufacturing process. (b) (4) was negative for genotoxicity by Ames and in vitro mouse lymphoma assays with crinecerfont drug substance spiked with (b) (4). The Applicant-proposed drug substance specification for this impurity is (b) (4)%, which is above the qualification threshold of (b) (4)%. The justification of specification of impurity is based on a 3-month toxicity study in rats. The (b) (4) was present at (b) (4)% in the crinecerfont batch used in the 3-month toxicity study in rats, which had a NOAEL of 500 mg/kg/day. The safety margin of (b) (4) for the proposed acceptance limit of (b) (4)% in crinecerfont drug substance was about (b) (4) based on body surface area (Table 137). The qualification data support the safety of (b) (4) at proposed acceptance limit of (b) (4)% in crinecerfont drug substance.

Table 137. Qualification of Impurity (b) (4) in Crinecerfont Drug Substance

Impurity	DS Spec (%)	% Impurity (DS Batch) ^a	NOAEL (mg/kg/day) (Species, Duration, Report)	Animal Exposure of Impurity at NOAEL (mg/kg/day) ^b	HED (mg/kg/day) ^c Based on BSA	Maximum Human Daily Exposure (mg/kg/day) ^d	Safety Margin ^e (b) (4)
(b) (4)							

Source: Compiled by reviewer

^a Impurity in DS lot used in toxicity study

^b Animal exposure = (%impurity*NOAEL)

^c HED at NOAEL in rat based on BSA

^d Maximum daily human exposure of impurity = (b) (4)

^e Safety margin = HED at NOAEL/human exposure at MRHD of 400 mg.

Abbreviations: BSA, body surface area; DS, drug substance; HED, human equivalent dose; MRHD, maximum recommended human dose; NOAEL, no-observed-adverse-effect level; Spec, specification

The impurity (b) (4) is an intermediate used in the synthesis of crinecerfont drug substance. (b) (4) was predicted positive for mutagenic potential by quantitative structural activity relationship. The Applicant proposed to control (b) (4) in the drug substance to the (b) (4) µg/day threshold of toxicological concern (TTC) level as a potential mutagenic impurity. Based on chronic administration limited to maximum (b) (4) µg/day (b) (4) and a maximum daily human dose of 400 mg crinecerfont, the proposed threshold limit of (b) (4) ppm for (b) (4) impurity is acceptable.

Process-related impurities (b) (4) were identified as mutagens by Ames test. The proposed control to limit the levels of these impurities in the drug substance to below

the TTC at (b) (4) ppm (b) (4) of the final drug substance is acceptable.

Impurity (b) (4) is an intermediate product of crinecerfont synthesis. (b) (4) was positive for skin sensitizing effect in local lymph node assay in mice but it was nonirritant to the skin or to the eye by primary irritation test in rabbits. The proposed acceptance criteria of (b) (4) % in drug substance specification is acceptable.

Extractables and Leachables

Crinecerfont oral solution (50 mg/mL, NDA 218820) is packaged in 2-oz polyethylene terephthalate (PET) bottles containing a minimum fill of 30 mL, fitted with heat-induction-sealed closure. The Applicant tested extractables and leachables for 50 mg/mL crinecerfont oral solution consistent with the study design that was agreed upon with the product quality team and DGE in prior communication. The study was conducted with 50 mg/mL crinecerfont oral solution packaged in 4-oz PET bottles with 75-mL fill. (b) (4)

The leachables study for crinecerfont oral solution in 4-oz bottles with caps was conducted using 3 drug product lots at proposed commercial storage conditions for ~14 months and the results showed that there were no compounds of toxicological concern leached into crinecerfont oral solution based on an analytical evaluation threshold of (b) (4) µg/mL drug product (200 mg/4 mL daily dose, (b) (4) µg/day TTC for chronic exposure (b) (4)

Immunotoxicity

The potential immunotoxicity of crinecerfont was evaluated by oral dosing of rats at 0, 15, 50 or 250 mg/kg/day for 28 days. Animals were immunized with keyhole limpet hemocyanin on Days 15 and 24 to assess the primary and secondary immune responses. Crinecerfont was associated with slight to moderate increase in lymphocytes, slight increase in B-cell count and slight increases in absolute CD3/CD4 T-cell count in females, and a slight decrease in T-cell-dependent antibody response in males. The changes in leukocytic parameters and lymphocyte subpopulation and T-cell-dependent antibody responses were small in magnitude and occurred in one sex (males) and showed no remarkable evidence of immunotoxicity in rats. Cyclophosphamide (positive control) induced marked immunotoxic effects, indicating the sensitivity of the assay.

Phototoxicity

A potential risk for phototoxicity of crinecerfont was evaluated in vitro using 3T3 cells at crinecerfont concentrations up to 20 µg/mL. No cytotoxicity was observed with or without ultraviolet A irradiation, indicating no phototoxic potential of crinecerfont. Chlorpromazine (positive control) induced a positive phototoxic effect, indicating the sensitivity of the assay.

Abuse Liability

Crinecerfont acts by inhibiting ACTH release from anterior pituitary, which is outside the blood-brain barrier. Tissue distribution studies following IV or PO administration in rats showed crinecerfont brain:plasma ratios of 0.1. The ex vivo binding studies following PO or IV dosing showed that crinecerfont was bound to CRF1 receptors both in pituitary and brain, with higher

percentage of CRF1 receptor occupancy in pituitary at early timepoints (0.5 to 1 hour postdose) than in brain and with similar levels of occupancy in later timepoints (2 to 24 hours postdose). Crinecerfont was not associated with clinical signs related to CNS effects in single- or repeat-dose toxicity studies in mice, rats, rabbits, and dogs dosed up to maximum tolerated doses. There was no evidence of a withdrawal syndrome during recovery periods of chronic toxicology studies in rats or dogs. Although the binding and tissue distribution studies were indicative of the potential for CNS effects, the series of single- and repeat-dose studies in multiple species indicated crinecerfont risk for potential for physical dependency is low.

19.2. Individual Reviews of Studies Submitted With the New Drug Application

Not applicable. Refer to Section [19.1](#).

20. Clinical Pharmacology

20.1. In Vitro Studies

20.1.1. Plasma Protein Binding in Rat, Mouse, Rabbit, Dog, and Human Plasma, Study LPR0879

The objective of this study was to assess plasma protein binding of crinecerfont tosylate in mouse, rat, rabbit, dog, and human plasma. Plasma samples from various species were spiked with [¹⁴C]-crinecerfont tosylate at 50, 500, 1000, 5000, 10000, and 30000 ng/mL and allowed to equilibrate for 1 hour. Specific binding of crinecerfont tosylate at 500 and 5000 ng/mL to human serum albumin and human serum α 1-acid glycoprotein was also determined. All studies were done in triplicate and radioactivity was determined by liquid scintillation counting. Results indicate that plasma protein binding was $\geq 99.9\%$ at concentrations above 50 ng/mL in all species evaluated. The mean percentage of binding of [¹⁴C]-crinecerfont tosylate to human serum albumin and α 1-acid glycoprotein for both concentrations tested was $>99.9\%$ and 96.6% , respectively. Thus, the in vitro studies indicate that crinecerfont is highly plasma protein bound and specifically binds albumin and α 1-acid glycoprotein.¹¹

20.1.2. Blood to Plasma Partitioning in Mouse, Rat, Dog, and Human Whole Blood, Study DPK0198

The objective of this study was to assess in vitro blood to plasma partitioning in mouse, rat, dog, and human whole blood. Whole blood samples from various species were spiked with [¹⁴C]-crinecerfont free base at 50, 500, 1000, 5000, 10 000 and 30 000 ng/mL and incubated for 0.5 hours. The blood/plasma and blood cells/plasma ratios were determined by assessing crinecerfont radioactivity by liquid scintillation counting. All studies were done in duplicate.

¹¹ Source: [LPR0879 Report](#)

Results indicate that whole blood/plasma ratios ranged from 0.5 to 0.7. Blood cell/plasma ratios were low across the species tested with human blood cell/plasma ratio of 0.08 ± 0.03 . Additionally, no concentration dependence was observed in terms of blood cell affinity at the concentration range evaluated.¹²

20.1.3. In Vitro Hepatic Clearance From Rat, Rabbit, Dog, and Human Hepatocytes, Study MIV0370

The objective of this study was to determine metabolic clearance of crinecerfont free base from fresh hepatocyte cultures obtained from rat, rabbit, dog, and humans. Crinecerfont free base was incubated for 24 hours at $1 \mu\text{M}$ in animal hepatocytes and 0.1 and $1 \mu\text{M}$ in human hepatocytes. Samples were obtained over 24 hours, supernatant and cellular homogenates were collected and analyzed by liquid-chromatography tandem mass spectroscopy (LC-MS/MS). All studies were done in triplicate. The in vitro intrinsic clearance (CL_{int}) values in rat, rabbit, dog, and human hepatocytes at $1 \mu\text{M}$ concentrations were 0.057 , 0.029 , 0.059 , and $0.028 \text{ mL/h}/10^6 \text{ cells}$, respectively. The CL_{int} at $0.1 \mu\text{M}$ in human hepatocytes was $0.029 \text{ mL/hr}/10^6 \text{ cells}$. Results indicate that the human hepatocytes were not saturable over the concentrations tested, and the CL_{int} from the hepatocytes of all the species tested was low and not concentration-dependent in human hepatocytes.¹³

20.1.4. In Vitro Metabolism in Mouse, Rat, Guinea Pig, Rabbit, Dog, Monkey, and Human Liver Microsomes, Study MIV0341

The objective of this study was to characterize the in vitro metabolism of [^{14}C]-crinecerfont in mouse, rat, guinea pig, dog, monkey, and human liver microsomes. [^{14}C]-crinecerfont tosylate at $5 \mu\text{M}$ and $25 \mu\text{M}$ was incubated up to 60 minutes in microsomes. All studies were done in triplicate and metabolite profiles were determined by high-performance liquid chromatography with an online radio-detection and metabolite structures were elucidated by LC-MS/MS. In vitro metabolism of [^{14}C]-crinecerfont tosylate was characterized at $5 \mu\text{M}$ (9.25 kBq/mL ; $0.25 \mu\text{Ci/mL}$), while the samples at $25 \mu\text{M}$ (18.5 kBq/mL ; $0.50 \mu\text{Ci/mL}$) were used for metabolite elucidation. Crinecerfont metabolism percentages were 5% in human, 12% in mouse, 14% in dog, 17% in rabbit, 26% in monkey, 56% in rat, and 61% in guinea pig. Excluding the rat and the guinea pig, metabolism of crinecerfont was slow. The rank order of liver metabolism in microsomes, from slowest to fastest, shows the following order: human < mouse $\approx$ dog $\approx$ rabbit < monkey << rat $\approx$ guinea pig. The primary metabolic pathways in humans were hydroxylation of the fluorophenyl moiety (M6) and N-dealkylation of the propargyl moiety (M4). Metabolites M6 and M4 constituted 4% and 3% of recovered drug material, respectively. Metabolites M6 and M4 were present in all the species tested.¹⁴

¹² Source: [DPK0198 Report](#)

¹³ Source: [Report MIV0370](#)

¹⁴ Source: [Report MIV0341](#)

20.1.5. In Vitro Metabolic Profile in Rabbit, Dog and Human Fresh Hepatocytes, Study MIV0358

The objective of this study was to assess the in vitro metabolism of [^{14}C]-crinecerfont in different animal species (rat, rabbit, dog) and human hepatocytes. Crinecerfont was assessed at 5 μM and 25 μM in hepatocytes for 24 hours at 37°C. Samples were assessed by high-performance liquid chromatography with an online radioactivity detector. Metabolites were elucidated using LC/MS. Crinecerfont was stable, with unchanged crinecerfont accounting for 82% of the recover drug-related material. The major metabolic pathways and metabolites identified from three human donors were named HH followed by number. These included hydroxylation on methyl of fluorophenyl moiety (HH7; M6 from study MIV0341), N-depropargylation (HH8) followed by hydroxylation (HH6; M4 from study MIV0341) and/or glucuronidation (HH3), hydroxylation on methyl-cyclopropane moiety followed by glucuronidation (HH5), and O-demethylation followed by glucuronidation (HH4) or followed by both hydroxylation and glucuronidation (HH2). Metabolites HH7, HH8, HH3, HH5, and HH4 were found in all the species tested. Metabolite HH6 was not detected in rabbits, metabolite HH4 was not detected in rats, and metabolite HH2 was not detected in dog. No interindividual variability was detected in the three tested human donors.¹⁵

20.1.6. In Vitro Metabolism in Human Liver Microsomes and Hepatocytes, Study MIH0179

The objective of this study was to assess the role of CYP450 enzymes on the metabolism of crinecerfont metabolism in human microsomes or from insect cells transfected with human CYP cDNA (Supersomes™) or cryopreserved human hepatocytes. In human microsomes, crinecerfont (0.1 and 1 μM) was incubated with or without a nicotinamide adenine dinucleotide phosphate (NADPH)-generating system for up to 60 min. In Supersomes, crinecerfont (0.1 and 1 μM) was incubated with or without an NADPH-generating system for 30 min. In human hepatocytes, crinecerfont (0.1 and 1 μM) was incubated with or without selective inhibitors of CYP2D6 (quinidine) or CYP3A (ketoconazole) for up to 6 hours. In human hepatocytes, bufuralol and midazolam metabolism were used as positive controls to confirm CYP2D6 and CYP3A activity. All samples were quantified using LC-MS/MS. In human liver microsomes, crinecerfont did not exhibit NADPH-dependent metabolism at 0.1 and 1 μM . In Supersomes, crinecerfont exhibited metabolism via CYP2B6, CYP2C8, CYP2C19 at both 0.1 and 1 μM concentrations. Additionally, crinecerfont at 0.1 μM concentration in Supersomes exhibited metabolism (to a lesser extent) by CYP2A6, and flavin-containing monooxygenases 1 and 2. In human hepatocytes, metabolism of crinecerfont was not inhibited by either quinidine (selective for CYP2D6) or ketoconazole (selective for CYP3A). Per the Applicant, the lack of metabolism by CYP2D6 and CYP3A is possibly because of the insolubility of crinecerfont in the heat-inactivated hepatocyte studies, given that the positive controls established activity for both enzyme isoforms. The Applicant concluded further investigation was necessary to determine the in vitro metabolism of crinecerfont.¹⁶

¹⁵ Source: [Report MIV0358](#)

¹⁶ Source: [Report MIH0179](#)

20.1.7. In Vitro Clearance and Fraction Metabolized by CYP3A in Human Hepatocytes Using Recombinant Human Enzymes, Study MIH0659

The objective of this study was to estimate the percentage of contribution of CYP enzymes identified in crinecerfont metabolism in Study MIH0179. At 0.1 or 10 μ M [¹⁴C]-crinecerfont concentrations, crinecerfont metabolism was assessed in human hepatocyte suspensions. Crinecerfont was incubated with and without 1 μ M ketoconazole (selective CYP3A inhibitor), or 1mM 1-Aminobenzotriazole (nonselective inhibitor of CYP3A4 and CYP2B6). An LC-MS/MS method was used to monitor the metabolism of crinecerfont depletion in hepatocytes and human liver microsomes (Supersomes). Crinecerfont concentrations in this study were 0.15 to 20 μ M to determine enzyme maximal velocity (V_{max}) and dissociation constant of the enzyme-substrate complex (K_m) for CYP2B6, CYP2C8, CYP2C19, and CYP3A4 in Supersomes. Metabolism of [¹⁴C]-crinecerfont did not occur in human hepatocyte suspensions at either 0.1 or 10 μ M and in vitro intrinsic clearance and estimations of fraction metabolized (f_m) by CYP3A could not be determined. In Supersomes, crinecerfont is metabolized primarily by CYP3A4 (estimated f_m ~68.0 to 83.7%) and, to a lesser extent, by CYP2B6 (estimated f_m ~10.7 to 25.2%). Contribution to crinecerfont metabolism from CYP2C8 and CYP2C19 was minor with estimated f_m values <5%.¹⁷

20.1.8. CYP450 Inhibition in Human Liver Microsomes, Study MIH0178

The objective of this study was to assess in vitro if crinecerfont inhibits CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A. Crinecerfont (200 μ M), microsomes, and NADPH were pre-incubated at 37°C for 15 min, then the CYP selective substrates for CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A were incubated at prespecified times to allow for product formation. LC-MS/MS was used to quantify the amount of product formed from each specific CYP assay. Crinecerfont at 200 μ M did not inhibit CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP3A. The estimated apparent inhibitor constant (K_i) values for these isoforms would be $\geq 233\mu$ M.¹⁸

20.1.9. Time-Dependent Inhibition of CYP450 Enzymes in Human Liver Microsomes, Study MIH0437

The objective of this study was to determine crinecerfont's potential to time-dependently inhibit CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A in human liver microsomes. Crinecerfont tosylate at 2.5 to 200 μ M or 1 to 25 μ M was added to liver microsomes and incubated for prespecified times with or without an NADPH-regenerating system, along with a selective substrate for a particular isoform. Isoform-selective inhibitors for CYP1A2, CYP2B6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 were furafylline, monoclonal antibody

¹⁷ Source: [Report MIH0659](#)

¹⁸ Source: [Report MIH0178](#)

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

2B6, sulfaphenazole, tranylcypromine, quinidine, monoclonal antibody 2E1, and ketoconazole, respectively. Parallel studies were conducted with crinecerfont.

All systems included a 30-minute preincubation period, except for CYP3B6 which had a preincubation time of 15 minutes, prior to the addition of the CYP selective substrate. Products formed were quantified using LC-MS/MS. Results indicate that preincubation with CYP2C19 and CYP3A in liver microsomes prior to the addition of selective isoform substrates showed greater inhibition than without preincubation indicating time-dependent inhibition. CYP2B6 and CYP2C9 also indicated a trend toward greater inhibition under preincubation conditions. No time-dependent inhibition was observed with CYP1A2, CYP2E1, or CYP2D6.¹⁹

20.1.10. Further Assessment on Time-Dependent Inhibition of CYP450 Enzymes in Human Liver Microsomes Identified in MIH0437, Study MIH0438

The objective of this study was to further assess the potential for crinecerfont tosylate to be a time-dependent inhibitor of CYP2B6, CYP2C9, CYP2C10, and CYP3A4 in liver microsomes.

Similar to Study MIH0437, crinecerfont tosylate at 25, 50, and 100µM was pre-incubated for 15 or 30 minutes with or without an NADPH-regenerating system. Postincubation aliquots were transferred to reaction mixtures containing the CYP isoform-specific substrates at their K_m concentrations along with a fresh NADPH-regenerating system. Selective mechanism-based inhibitors used included thio-TEPA (CYP2B6), tienilic acid (CYP2C9), ticlopidine (CYP2C19) and troleandomycin (CYP3A). Each assay was run for a prespecified time and metabolite concentrations were assessed using LC-MS/MS. Results indicate that under conditions evaluated, there was no significant time-dependent inhibition of CYP2B6, CYP2C9, or CYP2C19. Irreversible inhibition of CYP3A activity by crinecerfont between 25–100µM with 30-minute preincubation was observed in liver microsomes.

Further evaluation with CYP3A4 was performed to determine the kinetic constants, maximal rate of enzyme inactivation (K_{inact}), and the concentration of inhibitor that gives half-maximal rate of inactivation (K_i), for time-dependent inhibition of CYP3A4 by crinecerfont in liver microsomes expressing CYP3A4. The study design was similar to the one outlined in Section [20.1.9](#) above with additional preincubation times of 0, 10, 20, and 30 minutes and crinecerfont tosylate concentrations assessed included 0, 2.5, 5, 10, 15, 20, and 30µM. Testosterone was the substrate and the amount of 6β-hydroxytestosterone formed was quantified using LC-MS/MS. Results from this study determined that the apparent K_{inact} and K_i values for crinecerfont inhibition of recombinantly expressed CYP3A were 0.0408 min⁻¹ and 8.31µM, respectively. Based on the results from this study, crinecerfont irreversibly inhibited CYP3A activity when preincubated with liver microsomes for 30 minutes.²⁰

¹⁹ Source: [Report MIH0437](#)

²⁰ Source: [Report MIH0438](#)

20.1.11. CYP450 Inhibition in Human Liver Microsomes, Study MIH0507

The objective of this study was to assess crinecerfont free base inhibition of CYP2C8 in human liver microsomes. Human liver microsomes with an NADPH-regenerating system were incubated with paclitaxel at K_m , a selective CYP2C8 substrate, and crinecerfont free base between 0 to 200 μ M. The hydroxypaclitaxel formed was assessed by LC-MS/MS. Quercetin was used as a positive control as it is a selective CYP2C8 inhibitor. The IC_{50} values for CYP2C8 inhibition were calculated using WinNonlin Ver 5.2. The percent inhibition of CYP2C8 by crinecerfont at 10 μ M and ≥ 30 μ M were 33.9% and between 32.7 and 38.6%. The similarity in inhibition above 10 μ M is indicative of low crinecerfont solubility at higher concentrations. Based on the available data, the IC_{50} value of CYP2C8 was established as >10 μ M.²¹

20.1.12. CYP2C8 Time-Dependent Inhibition in Human Liver Microsomes, Study XT195084

The objective of this study was to assess the ability of crinecerfont to inhibit CYP2C8 in a time-dependent manner in human liver microsomes. Human liver microsomes with and without an NADPH-regenerating system were preincubated with or without crinecerfont 0.01 to 10 μ M and with and without selective inhibitors of CYP2C8 (montelukast (reversible) and gemfibrozil glucuronide (time-dependent)) for 30 minutes. Amodiaquine, a CYP2C8 substrate, was added to the preincubated samples and amodiaquine and its N-dealkylation metabolite concentrations were assessed by LC-MS/MS. Results indicate that crinecerfont directly inhibited CYP2C8 with a maximum inhibition of 44%. No change in percent inhibition was detected above 3 μ M up to 10 μ M and so the IC_{50} value was reported as >3 μ M. There was no evidence of time- or metabolism-dependent inhibition of CYP2C8 by crinecerfont as no change in percent inhibition was noted with and without preincubation with crinecerfont.²²

20.1.13. CYP1A2, CYP2C9, and CYP3A4 Induction in Human Hepatocytes, Study MIV0413

The objective of this study was to assess whether crinecerfont tosylate at 0.1, 1, 5, 10, and 50 μ M could induce CYP1A2, CYP2C9, and CYP3A4 gene expression and enzyme activity in fresh human hepatocytes. Human hepatocytes were incubated with crinecerfont tosylate for 72 hours, the level of induction was determined by evaluating gene expression using reverse transcription polymerase chain reaction, and enzyme activity was determined by activity using specific probe substrates. Positive inducer controls included in the study were β -naphthoflavone (50 μ M) for CYP1A2 and rifampicin (25 μ M) for CYP3A4 and CYP2C9. Crinecerfont concentrations at 50 μ M were found to be cytotoxic and were excluded from analysis. At concentrations up to 10 μ M, no induction of CYP1A2 in terms of gene expression or enzyme activity levels was observed. After 72 hours of exposure at 10 μ M crinecerfont, the level of CYP2C9 mRNA was increased by 1.9-fold (54% of reference inducer; rifampicin) and enzyme activity decreased to

²¹ Source: [Report MIH057](#)

²² Source: [Report XT195084](#)

28% of control. After 72 hours of exposure at 10µM crinecerfont, the level of CYP3A4 mRNA was increased by 26.6-fold (12% of reference inducer; rifampicin) and enzyme activity decreased to 56% of control. Overall, crinecerfont induced an increase in CYP2C9 and CYP3A4 gene expression but with an associated decrease in enzyme activity.²³

20.1.14. CYP2B6 Induction in Human Hepatocytes, Study XT183069

The objective of this study was to determine if crinecerfont is able to induce CYP2B6 gene expression and enzyme activity when treated with crinecerfont free base between 0.1 to 10µM in cryopreserved human hepatocytes. Crinecerfont was incubated in human hepatocytes for 72 hours and the level of induction was determined by reverse transcription polymerase chain reaction and enzyme activity on bupropion hydroxylation (probe substrate) (n=3). Controls included phenobarbital (1mM; positive control), and flumazenil (25µM; negative control). Treatment with up to 10µM crinecerfont resulted in concentration-dependent increases in CYP2B6 mRNA expression up to 3.25 to 5.15-fold in two of three cultures. The increase in mRNA expression in the two cultures was ≤2.6% of the positive control response. There was little or no induction of CYP2B6 activity (<2-fold change) following treatment with up to 10 µM crinecerfont for the third culture.²⁴

20.1.15. Permeability Assessment in Caco-2-TC7 Cells Expressing P-gp, Study AIV0071

The objective of this study was to assess the apparent permeability coefficient (P_{app}) of crinecerfont in Caco-2-TC7 cells and evaluate the role of P-gp in the absorption of crinecerfont. Caco-2-TC7 cells were seeded in 12-well plates, incubated at 37°C with 10% CO₂ and 95% relative humidity under a continuous gentle orbital agitation. The transport of [¹⁴C]-crinecerfont tosylate from apical to basal chamber was tested at 1µM (0.046 µCi/mL), 5µM (0.23 µCi/mL) and 20µM (0.92 µCi/mL) in the absence and in the presence of cells. Incubation time was 2 hours and at the end of the incubation time, samples were withdrawn from the apical and basolateral side and radioactivity was determined by liquid scintillation counting to determine P_{app} . Bidirectional transport (apical to basolateral and basolateral to apical) of 1, 5, and 20µM [¹⁴C]-crinecerfont tosylate across Caco-2-TC7 monolayers was performed to determine the role of P-gp in crinecerfont absorption. Controls for the P_{app} studies included [³H]-mannitol and high [¹⁴C]-testosterone, and the positive control for P-gp studies was [³H]-vinblastine. All studies were done in triplicate. The P_{app} of crinecerfont was 2.2×10^{-7} cm/s at 20µM and was similar to the low-permeability compound [³H]-mannitol, indicating the crinecerfont has a low permeability. Results for the P-gp studies indicate that the efflux ratio of crinecerfont was 0.9 at 20 µM and it is not considered a substrate for P-gp.²⁵

²³ Source: [Report MIV0413](#)

²⁴ Source: [Report XT183069](#)

²⁵ Source: [AIV0071 Report](#)

20.1.16. Crinecerfont Transporter Substrate Potential for BCRP, BSEP, OATP1B1, and OATP1B3, Study XT198097

The objective of this study was to assess the potential of crinecerfont (0.2, 1, 5, and 10 μ M) to be a substrate of transporters breast cancer resistance protein (BCRP), bile salt export pump (BSEP), organic anion transport polypeptide (OATP) 1B1, and OATP1B3. Substrate potential was defined as uptake or efflux ratio ≥ 2 that is reduced $>50\%$ in the presence of an inhibitor.

Crinecerfont potential as a substrate for BCRP was assessed using bidirectional permeability of in Madin-Darby canine kidney type II (MDCKII) cells with and without inhibitors (Ko143 and lopinavir). Samples were drawn from the receiver chamber over 120 minutes and concentrations were assessed by LC-MS/MS. In BCRP-expressing cells, the crinecerfont uptake could not be measured, due to poor permeability across these cells. Thus, crinecerfont potential as a substrate for BCRP could not be evaluated.

Crinecerfont potential as a substrate for BSEP was assessed by determining accumulation of crinecerfont in transporter-expressing vesicles with and without inhibitors (cyclosporine and glyburide) and with either ATP or AMP (negative control). At 1, 3, and 10 minutes crinecerfont accumulation in vesicles was assessed by LC-MS/MS. In BSEP vesicles, the crinecerfont uptake ratio was <2 compared to control at both 5 and 10 μ M concentrations, thus indicating that crinecerfont is not a substrate for BSEP.

Crinecerfont potential as a substrate for OATP1B1 and OATP1B3 was assessed by determining accumulation of crinecerfont in transporter-expressing human embryonic kidney (HEK) 293 cells with and without inhibitors (rifampin and cyclosporine). At 1, 3, and 10 minutes crinecerfont accumulation in vesicles was assessed by LC-MS/MS. In OATP1B3 cells, the crinecerfont uptake ratio was <2 compared to control at both 5 and 10 μ M concentrations, thus indicating that crinecerfont is not a substrate for OATP1B3. In OATP1B1 cells, the crinecerfont uptake ratio was >2 (range: 1.36 to 3.70). However, crinecerfont uptake was decreased by $<50\%$ in the presence of inhibitors of OATP1B1. Thus, overall, crinecerfont is not a substrate of OATP1B1 or OATP1B3.²⁶

20.1.17. P-gp Inhibition in Caco-2 Cells Expressing P-gp, Study AIV0107

The objective of this study was to assess if crinecerfont can inhibit P-gp transport of [^{3} H]-vinblastine in Caco-2-TC7 cells. Basal-to-apical transport and apical-to-basal transport of 5 μ M [^{3} H]-vinblastine in the absence (control) and in the presence of 0.1, 0.3, 1, 3, 10, 30 and 100 μ M crinecerfont was assessed over a 2-hour incubation period. Crinecerfont was added to both the apical and basal chambers. Verapamil (200 μ M) was used as the positive control for P-gp inhibition. Radioactivity in the samples was quantified by liquid scintillation. At 100 μ M crinecerfont precipitated and P-gp inhibition could not be quantified at this concentration. At

²⁶ Source: [Report XT198097](#)

crinecerfont concentrations up to 30µM, crinecerfont did not inhibit the net efflux of [³H]-vinblastine indicating the crinecerfont is not a P-gp inhibitor at the concentrations tested.²⁷

20.1.18. Crinecerfont Inhibition Potential for Transporters P-gp, BCRP, BSEP, OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K, Study XT188068

The objective of this study was to assess the potential of crinecerfont (10µM) to inhibit transporters P-gp, BCRP, BSEP, OATP1B1, OATP1B3, organic anion transporter (OAT) 1, OAT3, organic cation transporter (OCT) 2, multidrug and toxin extrusion transporter (MATE) 1, and MATE2-K.

P-gp inhibition was evaluated in Caco-2 cells and in MDCKII cells. Digoxin (10µM) was used as substrate for P-gp. The bidirectional permeability of the digoxin was assessed and quantified by LC-MS/MS. At 10µM crinecerfont, digoxin efflux ratio in Caco-2 cells decreased from 16.3 to 10.6, indicating a 37% inhibition in P-gp transport. At 10µM crinecerfont, digoxin efflux ratio in MDCKII-P-gp cells was not affected, indicating that in this system crinecerfont does not inhibit P-gp transport.

BCRP inhibition was evaluated in MDCKII cells. Prazosin (1µM) was used as substrate for BCRP. The bidirectional permeability of the prazosin was assessed and quantified by LC-MS/MS. At 10µM crinecerfont, the corrected prazosin efflux ratio in MDCKII-BCRP was not affected, indicating that crinecerfont does not inhibit BCRP.

Crinecerfont potential as an inhibitor of BSEP was assessed by determining accumulation of [³H]-taurocholic acid (0.4µM) by LC-MS/MS in transporter-expressing vesicles. At 10µM crinecerfont, the ATP-dependent uptake of [³H]-taurocholic acid (0.4µM) in BSEP vesicles did not decrease, indicating that crinecerfont is not an inhibitor of BSEP.

Crinecerfont potential as an inhibitor of OATP1B1, OATP1B3, OAT1, OAT3, OCT2, MATE1, and MATE2-K was assessed in HEK293 cells. OATP1B1, OATP1B3, MATE1, MATE2-K, and control cells were incubated with butyric acid (10mM) for 24 hours prior to the experiment to induce transporter gene expression. Crinecerfont 10µM, positive control, or negative control were preincubated for 15 minutes or 30 minutes before adding the probe substrate and incubating for 1 to 5 minutes. Probe substrates used for OATP1B1/B3, OAT 1, OAT 3, OCT2/MATE1/MATE2-K were [³H]-Estradiol- 17β-glucuronide (50nM), [³H]-p-aminohippurate (1µM), [³H]-estrone-3-sulfate (50nM), and [¹⁴C]-metformin (10µM), respectively. Positive controls used in this study were rifampin (10µM) and cyclosporine (1µM) for OATP1B1/B3; probenecid (100µM) and novobiocin (300µM) for OAT 1; probenecid (100µM) and ibuprofen (100µM) for OAT 3; quinidine (300µM) and cimetidine (2500µM) for OCT2; cimetidine (20µM) and pyrimethamine (0.5µM) for MATE1; and cimetidine (300µM) and pyrimethamine (3µM) for MATE2-K. Samples were quantified by liquid scintillation.

²⁷ Source: [Report AIV0107](#)

At 10 μ M crinecerfont:

- Uptake rate of [^{3} H]-estradiol-17 β -glucuronide (50nM) in OATP1B1 cells did not decrease, indicating that crinecerfont does not inhibit OATP1B1.
- Uptake rate of [^{3} H]-estradiol-17 β -glucuronide (50nM) in OATP1B3 decreased by 0.4%, indicating that crinecerfont likely does not inhibit OATP1B3.
- Uptake rate of [^{3} H]-p-aminohippurate (1 μ M) in OAT1 cells did not decrease, indicating that crinecerfont does not inhibit OAT1.
- Uptake rate of [^{3} H]-estrone-3-sulfate (50nM) in OAT3 cells did not decrease, indicating that crinecerfont does not inhibit OAT1.
- Uptake rate of [^{14} C]-metformin (10 μ M) in OCT2 cells was reduced by 2.2%, indicating that crinecerfont likely does not inhibit OCT2.
- Uptake rate of [^{14} C]-metformin (10 μ M) in MATE1 cells did not decrease, indicating that crinecerfont does not inhibit MATE1.
- Uptake rate of [^{14} C]-metformin (10 μ M) in MATE2-K cells did not decrease, indicating that crinecerfont does not inhibit MATE2-K.²⁸

20.2. In Vivo Studies

20.2.1. Single Ascending Dose Study of Crinecerfont Between 20 mg to 800 mg, Study TDU10479

Study Design

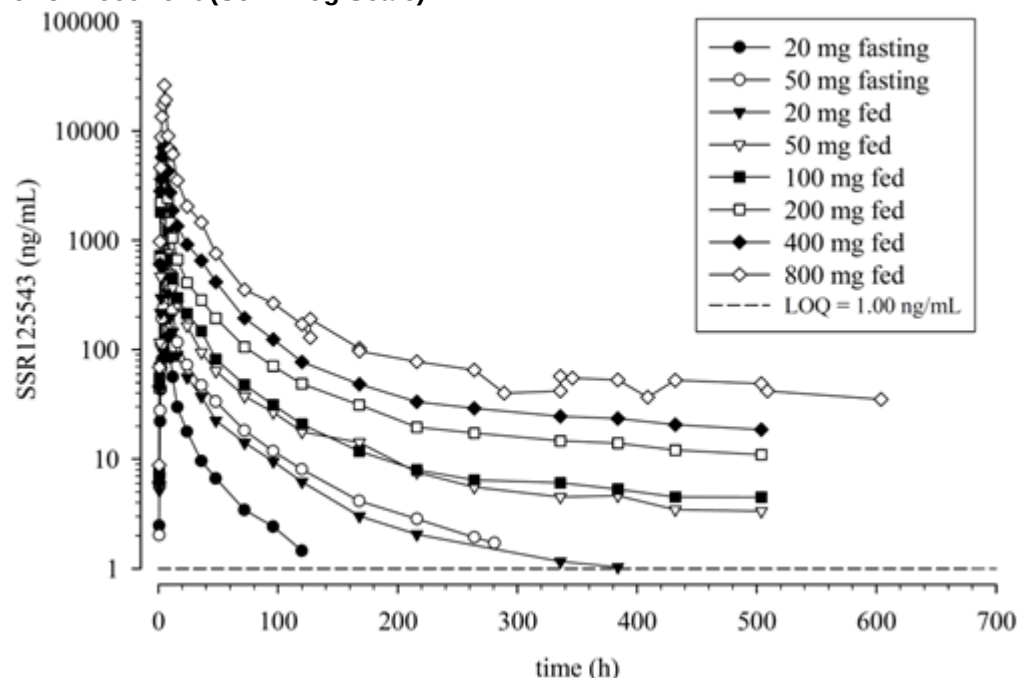
This is a phase 1 single oral ascending dose, safety, tolerability, and PK study of crinecerfont in healthy young male subjects. The primary objectives of this study were to assess safety and tolerability, and PK of single ascending doses of crinecerfont under fasted conditions or 30 minutes post moderate-fat breakfast. Subjects (n=6 per group) received oral doses of 20, 50, 100, 200, 400 or 800 mg crinecerfont or placebo and PK samples were obtained at prespecified time points over 504 hours. A total of 64 subjects were randomized with 48 subjects in the crinecerfont groups. Dropouts included three from the placebo group, one each from the 50 mg fasted and fed groups, and two each from the 100 mg fed and 800 mg fed groups primarily due to personal reasons. Crinecerfont PK parameters were calculated and 90% confidence intervals (CIs) for the geometric mean of fed versus fasted ratio for C_{max} , AUC, and $AUC_{0-tlast}$ were provided for each dose level. The food effect was determined at the 20 mg and 50 mg dose levels under fed and fasted conditions. Dose proportionality was assessed by regression analysis under fed conditions for C_{max} , $AUC_{0-tlast}$, and AUC.

²⁸ Source: [Report XT188068](#)

Results

The plasma time profile and PK parameters are presented in [Figure 34](#) and [Table 138](#), respectively. The median time to reach maximum observed plasma concentration (T_{max}) value was between 3 and 6 hours after a single dose of the drug between 20 to 800 mg. The apparent terminal elimination half-life was observed with mean values ranging from 188 to 464 hours (7.83 to 19.3 days) in fed condition.

Figure 34. Mean Crinecerfont Plasma Concentrations vs. Time Profiles After Single Administration of Crinecerfont (Semi-Log Scale)



Source: Figure 2, p. 61, Study TDU10479. [Link to CSR TDU10479](#)

Abbreviation: CSR, clinical study report; LOQ, limit of quantification; SSR125543, crinecerfont

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Table 138. Mean±SD (CV%) [Geometric Mean] of Crinecerfont (SSR125543) PK Plasma Parameters After Single Oral Administrations of Crinecerfont

PK Parameter	Crinecerfont Dose							
	20 mg Fasting	50 mg Fasting	20 mg Fed	50 mg Fed	100 mg Fed	200 mg Fed	400 mg Fed	800 mg Fed
*T _{max} (h)	6.00 (5.00, 6.07)	6.00 (5.00, 6.00)	5.00 (5.00, 5.00)	5.00 (2.50, 6.00)	3.00 (2.50, 6.00)	5.00 (3.00, 6.00)	4.50 (4.00, 6.05)	5.00 (5.00, 5.00)
C _{max} (ng/mL)	198±35.1 (18) [195]	741±516 (70) [629]	752±313 (42) [694]	1920±657 (34) [1820]	3840±1020 (27) [3710]	8830±2760 (31) [8470]	9750±3590 (37) [9250]	26100±5780 (22) [25500]
AUC _{last} (ng·h/mL)	2110±515 (24) [2060]	8620±6420 (74) [7160]	7550±3330 (44) [6770]	19600±10200 (52) [17800]	32000±6070 (19) [31500]	67500±22300 (33) [64300]	107000±31700 (30) [103000]	255000±64600 (25) [248000]
AUC (ng·h/mL)	2220±588 (27) [2160]	8870±6520 (73) [7410]	7950±3600 (45) [7090]	21000±10400 (50) [19200]	34400±5970 (17) [33900]	72300±24700 (34) [68600]	117000±35900 (31) [113000]	284000±65300 (23) [277000]
AUC ₂₄ (ng·h/mL)	1560±325 (21) [1530]	5470±3880 (71) [4600]	5090±2270 (44) [4580]	12000±6080 (51) [10900]	22600±5120 (23) [22000]	46000±11900 (26) [44600]	66000±16000 (24) [64400]	169000±4300 (20) [166000]
t _{1/2z} (h)	63.3±60 (94) [48.6]	130±62.8 (48) [118]	188±135 (72) [137]	311±81.7 (26) [302]	356±101 (28) [343]	303±45.8 (15) [300]	368±83.2 (23) [360]	464±265 (57) [406]

Source: Table 13, p. 63, Study TDU10479. [Link to CSR TDU10479](#)

Abbreviations: AUC, area under the concentration-time curve; C_{max}, maximum observed plasma concentration; CSR, clinical study report; CV, coefficient of variation; PK, pharmacokinetic; SD, standard deviation; t_{1/2z}, mean apparent terminal half-life; T_{max}, time to reach C_{max}

Point estimates with 90% CIs for the food effect at 20 mg and 50 mg are presented in [Table 139](#). Under fed conditions (moderate-fat breakfast) compared to fasted conditions, the $C_{\max}$ and AUC increased by approximately 3-fold.

Table 139. Point Estimates With 90% CI Interval for the Food Ratio

Parameter	Comparison	Estimate	90% CI
$C_{\max}$ (ng/mL)	Fed vs. fasted (overall)	3.21	(2.38-4.34)
	Fed vs. fasted (20 mg)	3.56	(2.32-5.45)
	Fed vs. fasted (50 mg)	2.90	(1.89-4.44)
AUC _{last} (ng·h/mL)	Fed vs. fasted (overall)	2.86	(2.02-4.05)
	Fed vs. fasted (20 mg)	3.29	(2.01-5.37)
	Fed vs. fasted (50 mg)	2.49	(1.52-4.07)
AUC (ng·h/mL)	Fed vs. fasted (overall)	2.92	(2.07-4.13)
	Fed vs. fasted (20 mg)	3.29	(2.01-5.36)
	Fed vs. fasted (50 mg)	2.60	(1.59-4.24)

Source: Table 14, p. 64, Study TDU10479. [Link to CSR TDU10479](#)

Abbreviations: AUC, area under the concentration-time curve; AUC_{last}, AUC from time 0 to the time of the last measurable concentration; CI, confidence interval; $C_{\max}$, maximum observed plasma concentration; CSR, clinical study report

Dose proportionality assessment by regression analysis from 20 mg to 800 mg (40-fold dose increase) indicates that the $C_{\max}$, AUC_{0-tlast} and AUC increased by 31.7, 32.8 and 34.5, respectively (data not shown).

Conclusions

- The apparent terminal elimination half-life of crinecerfont was long and ranged from 7.8 to 19.3 days under fed conditions.
- Under fed conditions at 20 mg and 50 mg of crinecerfont, the $C_{\max}$, AUC, and AUC_{0-tlast} increased by approximately 3-fold.
- Crinecerfont was roughly dose proportional between 20–800 mg.

20.2.2. Crinecerfont Capsule Dose Linearity 20 mg to 200 mg, Study TDR10671

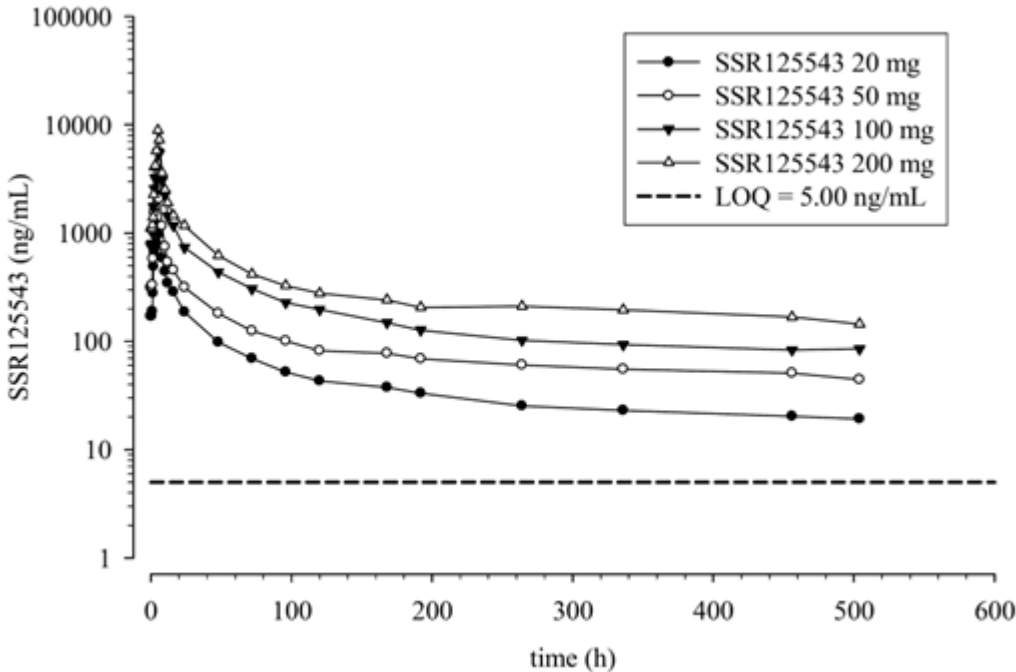
Study Design

This is a phase 1, randomized, double-blind, placebo-controlled study of the tolerability and pharmacokinetics of 14-day repeated ascending oral doses of crinecerfont in 48 healthy young male subjects. The primary objectives of this study were to assess the tolerability, safety, and pharmacokinetics after repeated oral ascending doses of crinecerfont. Crinecerfont was administered at 20, 50, 100, and 200 mg under fed-conditions (moderate-fat breakfast) every day for 14 days. A total of 48 subjects were enrolled, with 32 subjects in the treatment group (all subjects in the treatment group completed the study). Dropouts included 4 in the placebo group. PK samples were obtained at prespecified time points over 504 hours. PK parameters were calculated from plasma concentrations of crinecerfont and time to steady state, dose proportionality, and accumulation ratio were calculated.

Results

The mean plasma concentrations of crinecerfont versus time on Day 14 after repeated once-daily oral administration of crinecerfont for 14 days are presented in [Figure 35](#). PK analysis indicates that the mean terminal elimination half-life was approximately 20.6 days over the 20–200 mg dose range (data not shown). Accumulation ratio was assessed by linear fixed model and estimates of accumulation ratio with 90% CI are presented in [Table 140](#).

Figure 35. Mean (±SD) Plasma Concentration of Crinecerfont vs. Time Profiles on Day 14 (Semi-Log Scale)



Source: Figure 11, p. 91, Study TDR10672. [Link to CSR 10672](#)
Abbreviations: CSR, clinical study report; LOQ, limit of quantification; SD, standard deviation; SSR125543, crinecerfont

Table 140. Estimates of Accumulation Ratio With 90% CI

Parameter	Group/Comparison	Estimate	90% CI
Rac (AUC ₂₄)	Pooled SSR125543 doses	1.44	(1.36-1.53)
	SSR125543 20 mg	1.58	(1.39-1.78)
	SSR125543 50 mg	1.42	(1.27-1.60)
	SSR125543 100 mg	1.52	(1.36-1.71)
	SSR125543 200 mg	1.26	(1.12-1.42)
Rac (C _{max})	Pooled SSR125543 doses	1.23	(1.15-1.32)
	SSR125543 20 mg	1.24	(1.07-1.42)
	SSR125543 50 mg	1.21	(1.05-1.39)
	SSR125543 100 mg	1.33	(1.16-1.53)
	SSR125543 200 mg	1.17	(1.01-1.34)

Source: Table 29, p. 96, Study TDR10672. [Link to CSR 10672](#)
Abbreviations: AUC₂₄, area under the concentration-time curve from 0 to 24 hours; CI, confidence interval; C_{max}, maximum observed plasma concentration; Rac, accumulation ratio; SSR125543, crinecerfont

Dose proportionality for C_{max} and AUC₂₄ of crinecerfont was evaluated for Day 1 and Day 14 separately using a log transformed power model. The data for estimates with 90% CI for r-fold increases in dose are presented in [Table 141](#).

Table 141. Dose Proportionality Assessment, Estimates With 90% CI for r-Fold Increases

		Ratio	
Parameter	Dose Ratio	Estimate	90% CI
Day 1			
C _{max} (ng/mL)	(r)=2	1.90	(1.73-2.07)
	(r)=10	8.37	(6.23-11.24)
	Beta estimate	0.92	(0.79-1.05)
AUC ₂₄ (ng·h/mL)	(r)=2	1.84	(1.69-2.02)
	(r)=10	7.65	(5.66-10.32)
	Beta estimate	0.88	(0.75-1.01)
Day 14			
C _{max} (ng/mL)	(r)=2	1.88	(1.74-2.04)
	(r)=10	8.18	(6.28-10.65)
	Beta estimate	0.91	(0.80-1.03)
AUC ₂₄ (ng·h/mL)	(r)=2	1.79	(1.63-1.97)
	(r)=10	6.96	(5.07-9.55)
	Beta estimate	0.84	(0.70-0.98)

Source: Table 27, p. 95, Study TDR10672. [Link to CSR 10672](#).

Abbreviations: AUC₂₄, area under the concentration-time curve from 0 to 24 hours; CI, confidence interval; C_{max}, maximum observed plasma concentration

Conclusions

- Steady state was reached in 7 days and with a mean accumulation ratio of 1.23 for C_{max} and 1.44 for AUC₂₄ indicating drug accumulation is low.
- Crinecerfont exposure, as measured by AUC₂₄ was approximately 7-fold and dose-proportional between 20–200 mg (10-fold dose increase) after steady state is achieved.

20.2.3. Mass Balance, Excretion, and Metabolite Profiling, Study BEX5094

Study Design

This is a phase 1, open-label, nonrandomized, single-dose study to determine the excretion balance and pharmacokinetics after oral administration of 100 mg of [¹⁴C]-crinecerfont to healthy male subjects.

Objectives

- Determine the excretion balance and systemic exposure of radioactivity after oral administration of [¹⁴C]-crinecerfont.
- Determine pharmacokinetics of crinecerfont and its contribution to overall exposure.
- Determine metabolic pathways of crinecerfont and identify the chemical structures of the main metabolites.

The study enrolled six subjects, five completed the study and one was lost to follow-up. Crinecerfont was administered with a high-fat breakfast as two 50 mg capsules containing a total dose of 100 mg crinecerfont with 2.59 MBq (70 µCi) [¹⁴C]-crinecerfont. PK samples were obtained at prespecified time points over 37 days in whole blood, plasma, urine, feces, and expired air. PK parameters, C_{max}, T_{max}, AUC_{last}, AUC_{0-∞}, and t_{1/2}, and blood to plasma

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radioactivity ratio were calculated at each time point. Metabolic profiling following single oral administration of [^{14}C]-crinecerfont (100 mg, 2.59 MBq) to healthy male subjects from plasma, urine and feces samples was also performed. Determination of radioactivity was carried out using liquid scintillation counting, either directly or after combustion.

Results

PK parameters and total radioactivity recovered in plasma and whole blood are presented in [Table 142](#). Based on the total radioactivity recovery in plasma for C_{max} and AUC_{24} there is low likelihood of metabolites. The mean apparent terminal half-life ($t_{1/2z}$) was 19.9 days.

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Table 142. Crinecerfont (SSR125543) PK Parameters and Total Radioactivity in Plasma and Blood (n=6)

Parameter	SSR125543	Total Radioactivity		Ratio (%)	
	Plasma	Plasma	Whole Blood	Plasma SSR125543/ Total Radioactivity	Whole Blood/ Plasma Total Radioactivity
C _{max} (ng/mL or ngEq/mL)	4820 (18) [3980-5910]	4690 (15) [3770-5670]	2380 (12) [2090-2770]	103 [92.7-111]	51.0 [47.9-56.0]
T _{max} (h)	5.00 [4.05-6.00]	5.00 [4.05-6.00]	5.00 [4.05-6.00]		
t _{last} (h)	756 [504-864]	336 [336-840]	168 [96-168]		
AUC ₂₄ (ng·h/mL or ngEq·h/mL)	34600 (21) [26700-46200]	35300 (19) [29700-46100]	18300 (20) [15400-24300]	97.6 [89.8-100]	51.7 [46.7-53.5]
AUC _{last} (ng·h/mL or ngEq·h/mL)	58000 (25) [47000-83900]	70300 (29) [56800-109000]	30000 (25) [23100-42800]	79.3 ^a [73.7-84.9]	52.5 ^a [48.8-54.8]
AUC (ng·h/mL or ngEq·h/mL)	63300 (23) [51500-89100]	83600 (31) [65000-132000]	34200 (27) [24800-48900]		
t _{1/2z} (h)	477 (45) [238-878]	325 (65) [163-610]	76.4 (50) [27.0-111]		

Source: Table 8, p. 45. Study BEX5094. [Link to CSR BEX5094](#)

Abbreviations: AUC, area under the concentration-time curve; AUC_{last}, AUC from time 0 to the time of the last measurable concentration; AUC₂₄, AUC from 0 to 24 hours; C_{max}, maximum observed plasma concentration; CSR, clinical study report; PK, pharmacokinetic; t_{last}, time of last measurable observed concentration; T_{max}, time to reach C_{max}; t_{1/2z}, mean apparent terminal half-life

[Table 143](#) presents excretion balance and recovery of radioactivity from urine, feces, and expired air. Most of the dose recovered in 37 days was from feces. Due to the long apparent terminal half-life of 19.9 days the total amount of radioactivity recovered over 37 days was 49.4%.

Table 143. Excretion Balance and Recovery of Radioactivity Within 37 Days^a (% of Administered Dose)

Subject No.							
Parameter	(b) (6)						Mean (CV%)
Urine	2.16	1.52	2.15	1.65	2.17	2.23	1.98 (16)
Feces	40.5	44.4	41.6	50.2	49.8	57.3	47.3 (13)
Expired CO ₂	0.13	0.16	0.13	0.17	0.14	0.17	0.150 (13)
Total	42.8	46.1	43.9	52.0	52.1	59.6	49.4 (13)

Source: Table 9, p. 46, Study BEX5094. [Link to CSR BEX5094](#)

Abbreviations: CSR, clinical study report; CV, coefficient of variation

Metabolic profiling following single oral administration of [¹⁴C]-crinecerfont (100 mg, 2.59 MBq) indicated the presence of 18 metabolites. In human plasma, parent crinecerfont was the main circulating compound (average 92% recovered radioactivity). Five metabolites were identified with the main metabolite being SAR274358 (M6; NBI-756179). [Table 144](#) presents the major metabolites recovered in the study. No metabolites were recovered in the urine. Approximately 2.7% of the parent compound was recovered in the feces indicating that the parent compound is metabolized. Per the Applicant, “The low recovery of total radioactivity in this study is attributed primarily to prolonged tissue retention and slow elimination of radioactivity that is rate-limited by redistribution from tissues. The presence of remaining drug-related material at the end of the 37-day collection period is supported by the fact that crinecerfont was quantifiable in plasma by LC-MS/MS in all subjects up to the time of the last blood sample collection (21 to 35 days).”

Table 144. Plasma Metabolites Expressed as Percent of Total Radioactivity and Relative to Parent Drug Following a Single Oral Administration of [¹⁴C]-Crinecerfont to Healthy Subjects

Compound	Percent of Radioactivity						AUC** (ngEq·h/mL)
	5h	12h	24h	48h	96h	144h	
SSR125543	95.6	87.1	83.0	76.7	61.0	54.1	57045
M4 = SR126862 (N-depropargylation cyclopropylethane)	1.1	1.6	2.2	2.7	nd	nd	
M6 = SAR274358 (fluoro phenyl hydroxylation)	1.5	7.4	10.8	14.7	29.6	30.3	8223 ^[1]
M7*	1.5	1.2	nd	nd	nd	nd	
M9 (N-depropargylation of SAR274358)	nd	1.6	2.4	3.6	6.4	nd	
M11 (O-demethylation of SAR274358)	nd	1.2	1.0	1.5	nd	nd	
Total radioactivity (ngEq/mL)	4568	1177	536	266	107	63.0	68660

Compound	Percent of Radioactivity						AUC** (ngEq·h/mL)
	5h	12h	24h	48h	96h	144h	
LOD	0.5	0.9	1.0	1.2	6.1	13.1	
Extraction yield (%)	94	96	87	85	104	72	

Source: Compiled from Table 1, p. 26, Study MEH0049. [Link to CSR MEH0049](#)

* Not identified

** AUC extrapolated to infinity

[1] 14.4% of parent AUC**

Abbreviations: AUC, area under the concentration-time curve; CSR, clinical study report; LOD, limit of detection; M(X), metabolite (X =4, 6, 7, 9, 11); nd, below the LOD; SSR125543, crinecerfont

Conclusions

- Following a single dose of 100 mg crinecerfont, with 2.59 MBq (70 µCi) [¹⁴C]-crinecerfont, only 49.4% of the administered dose was recovered.
- The total mean amount of radioactivity recovered in the feces over 37 days was 47.3% of the administered dose. Approximately 2.7% of the parent compound was recovered in the feces indicating that the parent compound is extensively metabolized.
- The total amount of radioactivity recovered in the urine over 37 days was <2% of the administered dose.
- An abundant metabolite, M6, constituting 14.4% of the parent AUC was identified. All other metabolites represented <6% of the parent compound.
- The M6 metabolite has a high affinity for CRF1 with K_i of 1.14nM, similar to crinecerfont affinity (0.6 to 3.99nM). However, in vivo, due to its limited exposure at steady state in humans (approximately 6% relative to crinecerfont), M6 is not expected to significantly contribute to the clinical CRF1 inhibition profile.

20.2.4. Development of (b) (4) Capsule Formulation, Study GAR6751

Study Design

This is a phase 1, open-label, randomized, parallel group, single-sequence, two-period crossover per group study. The primary objectives of this study were to assess the food effect on PK profiles of four capsule formulations of crinecerfont and assess the relative bioavailability of three (b) (4) capsule formulations of crinecerfont versus a (b) (4) capsule formulation of crinecerfont. A total of 49 healthy male subjects were enrolled and 48 completed the study. Subjects were randomized into four treatment groups and were given each treatment under fasted and fed conditions (high-fat breakfast) with a 14-day washout period between the treatments.

- Treatment A = (b) (4) capsule formulation A, strength of 50 mg → CL-10257
- Treatment B = (b) (4) capsule formulation B, strength of 50 mg → CL-10342
- Treatment C = (b) (4) capsule formulation C, strength of 50 mg → CL-10336
- Treatment D = (b) (4) capsule formulation D, strength of 100 mg → CL-09333

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

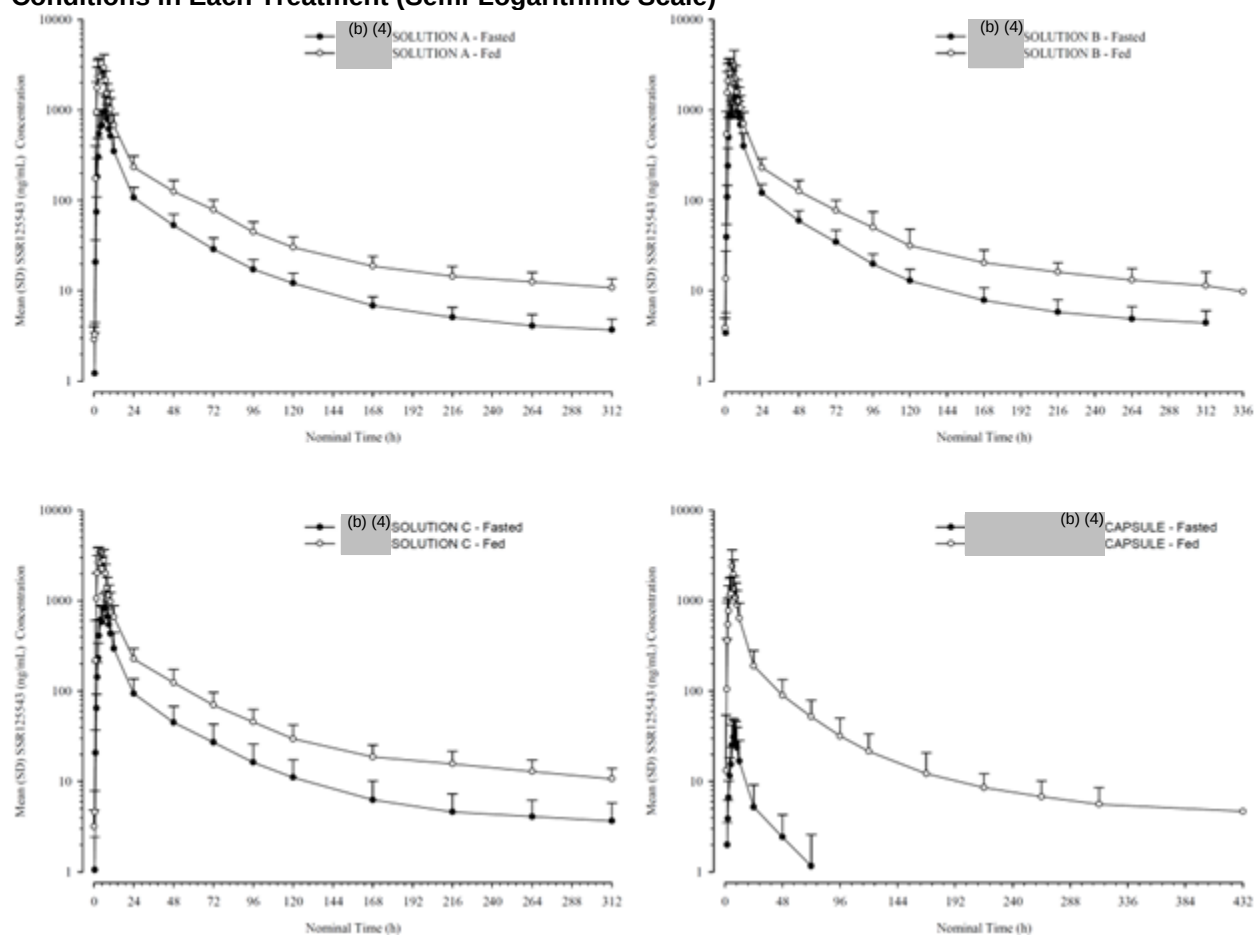
PK samples were obtained at prespecified time points over 312 hours. Geometric mean ratios (GMRs) with 90% CIs were calculated and compared for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} comparing the food effect for each formulation and for formulation effect in a pairwise manner as compared to the reference formulation (treatment D).

Results

Food Effect

The effect of food within each treatment group is presented in [Figure 36](#).

Figure 36. Mean (+SD) Plasma Concentration vs. Time Curves of Crinecerfont In Fed vs. Fasted Conditions in Each Treatment (Semi-Logarithmic Scale)



Source: Figure 5, p. 50, Study GAR6751. [Link to CSR GAR6751](#)
Abbreviations: CSR, clinical study report; SSR125543, crinecerfont

Formulation Effect

The GMR estimates and 90% CIs of crinecerfont PK parameters comparing formulations A-C to reference formulation (D) in fasted and fed conditions are presented in [Table 145](#).

Table 145. GMR Estimates and 90% CI Values for Pairwise Comparison Between Test Formulations (A-C) and Reference Formulation (D)

Comparison	AUC _{0-t_{last}} (ng·hr/mL)		AUC _{0-∞} (ng·hr/mL)		C _{max} (ng/mL)	
	GMR	90% CI	GMR	90% CI	GMR	90% CI
A/D – fasted	36.4	27.5, 48.1	32.4	24.0, 43.7	37.1	27.4, 50.3
A/D – fed	1.48	1.12, 1.96	1.61	1.22, 2.12	1.49	1.10, 2.02
B/D – fasted	44.9	34.2, 59.0	39.9	29.7, 53.5	48.9	36.3, 65.8
B/D – fed	1.56	1.18, 2.06	1.60	1.21, 2.10	1.55	1.15, 2.10
C/D – fasted	31.2	24.0, 41.2	28.4	21.0, 38.3	31.1	22.9, 42.1
C/D – fed	1.51	1.14, 2.00	1.56	1.19, 2.06	1.54	1.14, 2.09

Source: Compiled from Tables 9 and 10, p. 55, Study GAR6751. [Link to CSR GAR6751](#)

Abbreviations: AUC, area under the concentration-time curve; AUC_{0- t_{last}} , AUC from time 0 to the time of the least measurable concentration; AUC_{0- ∞} , AUC from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CSR, clinical study report; GMR, geometric mean ratio

Conclusions

- Food effect
 - When crinecerfont is taken with a high-fat breakfast as compared to fasted conditions both AUC and C_{max} increased by approximately 3-fold.
- Formulation effect
 - Administration with a high-fat meal resulted in the three (b) (4) formulations (A-C) having approximately 1.5-fold higher AUC and C_{max} compared to the reference (b) (4) capsule.
 - Administration under fasted conditions resulted in the three (b) (4) formulations (A-C) having approximately 30- to 40-fold higher AUC and C_{max} values as compared to the reference (b) (4) capsule.
- No significant differences were noted in the three (b) (4) formulations tested.

20.2.5. Hepatic Impairment Study, Study NBI-74788-1717

Study Design

This is a phase 1, single-dose, open-label study designed to assess the safety, tolerability, and pharmacokinetics of crinecerfont and its metabolites in subjects with mild, moderate, or severe stable chronic hepatic impairment relative to subjects with normal hepatic function. The primary objective of this study was to assess the pharmacokinetics of crinecerfont (NBI-74788) and its metabolite (NBI-7456179; M6) in subjects with normal, mild, moderate, and severe hepatic impairment. Hepatic impairment was defined using the Child-Pugh scale. A total of 25 adult subjects between the ages of 18–75 years were enrolled. The normal, mild, and moderate groups had six subjects each while the severe hepatic impairment group had seven subjects. The group

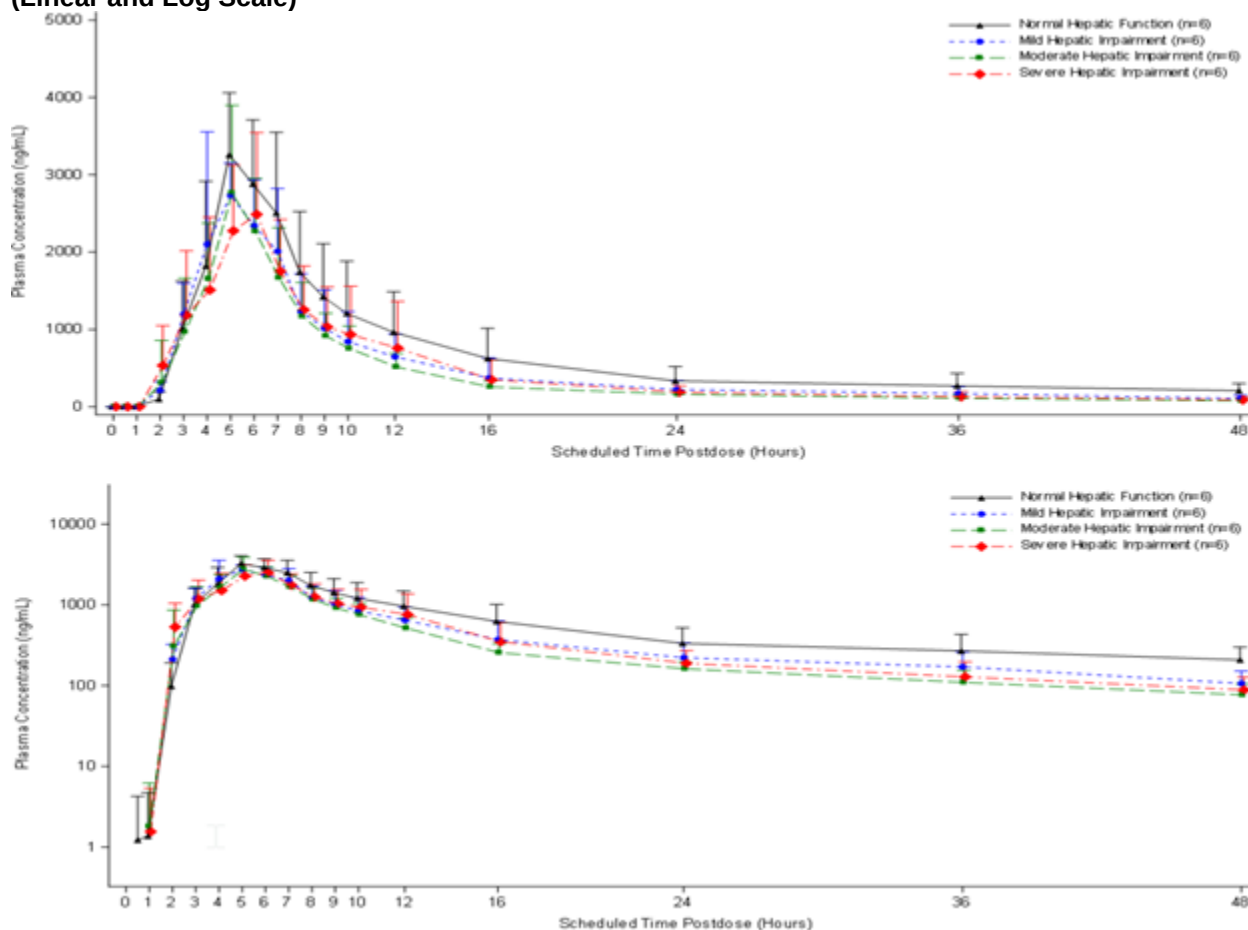
of subjects with normal hepatic function were similar in age (± 5 years), sex, race, and weight ($\pm 10\%$) to the subjects with hepatic impairment. An overnight fast of 10 hours was followed by the administration of two 50 mg crinecerfont capsules with 237 mL of Ensure Plus and 120 mL of water. PK samples were obtained at prespecified time points over 504 hours. GMRs with 90% CIs were calculated and compared for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} in the mild, moderate, and severe hepatic impairment groups to the reference normal group. All subjects completed the study.

Results

The mean plasma crinecerfont concentrations versus time in subjects with normal, mild, moderate, and severe hepatic impairment are presented in [Figure 37](#). The mean apparent terminal half-life ($\pm$ standard deviation [SD]) of crinecerfont in normal mild, moderate, and severe hepatic impairment were 136 h (96.0), 87.2 h (71.3), 119 h (34.9), and 221 h (87.1), respectively. In subjects with severe hepatic impairment, apparent terminal half-life did increase, however, the increase is not significant due to the large standard deviation associated with this parameter.

The effective half-life of crinecerfont is ~ 14 hours and a PK sampling time of 504 hours is appropriate as it covers more than five half-lives. Comparison of GMRs with the 90% CIs for $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} for 100 mg crinecerfont and its metabolite M6 in the different hepatic impairment groups are presented in [Table 146](#).

Figure 37. Mean (+SD) Crinecerfont Plasma Concentrations vs. Time by Hepatic Function Group (Linear and Log Scale)



Source: Figure 2, p. 35. Study NBI-74788-1717. [Link to CSR 1717](#)
Abbreviations: CSR, clinical study report; SD, standard deviation

Table 146. Crinecerfont (100 mg) and Its Metabolite M6 GMR and 90% CI PK Exposure Parameters Comparing Mild, Moderate, and Severe Hepatic Impairment Groups to the Normal Hepatic Function Group

Comparison	Crinecerfont			M6		
	AUC _{0-tlast}	AUC _{0-∞}	C _{max}	AUC _{0-tlast}	AUC _{0-∞}	C _{max}
	(ng·hr/mL)	(ng·hr/mL)	(ng/mL)	(ng·hr/mL)	(ng·hr/mL)	(ng/mL)
	GMR	GMR	GMR	GMR	GMR	GMR
	(90% CI)	(90% CI)	(90% CI)	(90% CI)	(90% CI)	(90% CI)
Mild hepatic impairment vs. normal hepatic function	0.73 (0.48, 1.11)	0.73 (0.48, 1.12)	0.91 (0.68, 1.23)	0.65 (0.45, 0.95)	0.62 (0.40, 0.96)	0.75 (0.49, 1.12)
Moderate hepatic impairment vs. normal hepatic function	0.66 (0.44, 1.01)	0.66 (0.43, 1.00)	0.85 (0.63, 1.14)	0.55 (0.38, 0.80)	0.57 (0.37, 0.89)	0.49 (0.32, 0.74)
Severe hepatic impairment vs. normal hepatic function	0.76 (0.50, 1.16)	0.80 (0.53, 1.22)	0.83 (0.62, 1.11)	0.34 (0.24, 0.50)	0.36 (0.23, 0.58)	0.29 (0.19, 0.45)

Source: Compiled from Table 6 (p. 37), and table 8 (p.41) Study NBI-74788-1717. [Link to CSR 1717](#)

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-tlast}, AUC from time 0 to the time of the least measurable concentration; AUC_{0-∞}, AUC from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CSR, clinical study report; GMR, geometric mean ratio; PK, pharmacokinetic

Conclusions

- Overall, the mild, moderate, and severe hepatic impairment groups had lower $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} compared to subjects with normal hepatic function. The magnitude of impact on crinecerfont pharmacokinetics seems to be comparable between mild and severe hepatic impairment. The mechanism of decreased crinecerfont exposures due to hepatic impairment is not known. However, the 90% CI values for the GMRs all included unity indicating that while the PK exposure is lower it does not appear to be clinically significant.
- There were no deaths, severe adverse events (AEs), or discontinuations from the study due to AEs reported in this study. No safety concerns related to routine clinical laboratory results, vital signs, or electrocardiogram results were identified.

Metabolite M6 has a similar affinity for the CRF1 compared to the parent drug. However, due to limited systemic exposure (i.e., approximately 6% relative to crinecerfont), M6 is not expected to significantly contribute to the pharmacological activity of crinecerfont.

20.2.6. Extrinsic Factors: Rifampin Study, Study NBI-74788-1718

Study Design

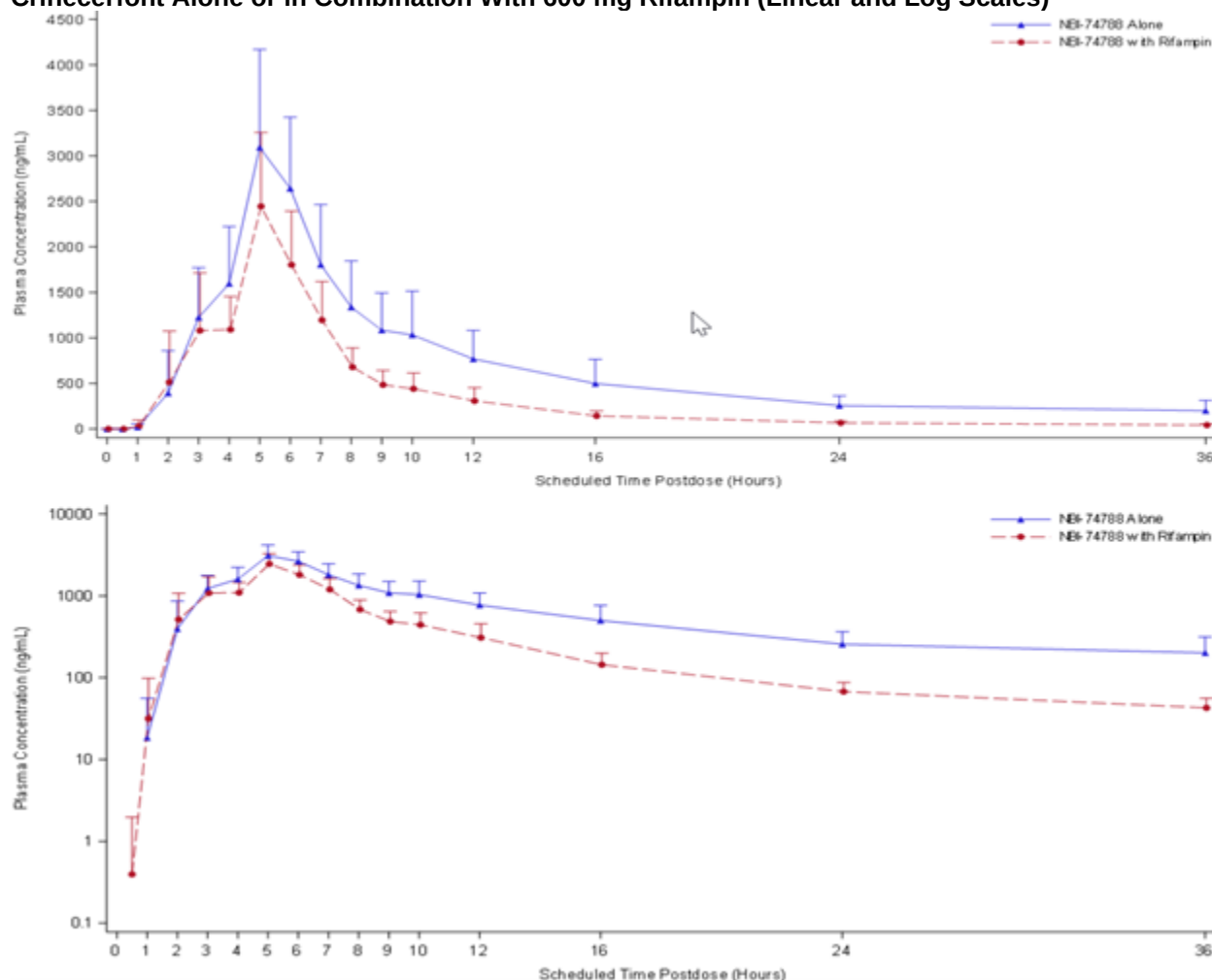
This is a phase 1, open-label, one-sequence crossover study to assess the effect of rifampin on the pharmacokinetics of crinecerfont (NBI-74788) in healthy subjects. The primary objective of this study is to evaluate and compare the pharmacokinetics of crinecerfont when crinecerfont is administered alone and concomitantly with rifampin. A total of 16 adult subjects between the ages of 18–55 years were enrolled. In treatment period 1, a single oral dose of 100 mg crinecerfont was administered with 237 mL Ensure Plus following a 10 hour overnight fast. Following a 21-day washout period, treatment period 2 commenced with subjects receiving 600 mg rifampin once daily for 29 days in the fasted state. On Day 9 of period two subjects received crinecerfont 2 hours after rifampin dosing with 237 mL Ensure Plus. PK samples were obtained at prespecified time points over 504 hours for crinecerfont and its major metabolite NBI-756169. GMRs with 90% CIs were calculated and compared for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} for crinecerfont with rifampin versus reference (crinecerfont alone). All subjects completed the study.

Results

The PK profile of 100 mg crinecerfont with and without rifampin 600 mg is presented in [Figure 38](#). Comparison of GMRs with the 90% CIs for $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} for 100 mg crinecerfont with rifampin and crinecerfont alone are presented in [Table 147](#).

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CRENESSITY (crinecerfont) oral capsule and oral solution

Figure 38. Mean ($\pm$ SD) Crinecerfont Plasma Concentrations vs. Time for Treatment With 100 mg Crinecerfont Alone or in Combination With 600 mg Rifampin (Linear and Log Scales)



Source: Table 4, p.38, Study NBI-74788-1718. [Link to CSR 1718](#)
Abbreviations: CSR, clinical study report; SD, standard deviation

Table 147. PK Exposure Parameters, GMR, and 90% CI Comparing 100 mg Crinecerfont With Rifampin and 100 mg Crinecerfont Alone

Parameter	Crinecerfont 100 mg	Crinecerfont 100 mg + Rifampin 600 mg	GMR (90% CI)
	Geometric Mean (CV%)	Geometric Mean (CV%)	
AUC _{0-tlast} (ng·hr/mL)	37300 (43.9)	13000 (24.8)	0.37 (0.33, 0.42)
AUC _{0-inf} (ng·hr/mL)	38400 (43.8)	13600 (24.1)	0.38 (0.33, 0.43)
C _{max} (ng/mL)	3290 (28.2)	2530 (28.6)	0.77 (0.67, 0.89)

Source: FDA reviewer table from Table 3, p. 37 and Table 4, p.38, Study NBI-74788-1718. [Link to CSR 1718](#).
Abbreviations: AUC, area under the concentration-time curve; AUC_{0-tlast}, AUC from time 0 to the time of the least measurable concentration; AUC_{0-inf}, AUC from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CSR, clinical study report; CV, coefficient of variation; GMR, geometric mean ratio; PK, pharmacokinetic

Conclusions

- The study is appropriately designed to determine if induction of CYP3A4 by a strong inducer, rifampin, decreases crinecerfont exposure.
- The mean $AUC_{0-t_{last}}$ and $AUC_{0-\infty}$ decreased by approximately 60% when crinecerfont is co-administered with rifampin 600 mg. Approximately 20% decrease in C_{max} is observed in the crinecerfont and rifampin group compared to the crinecerfont group alone.

20.2.7. Extrinsic Factors: Ketoconazole Study, Study INT5449

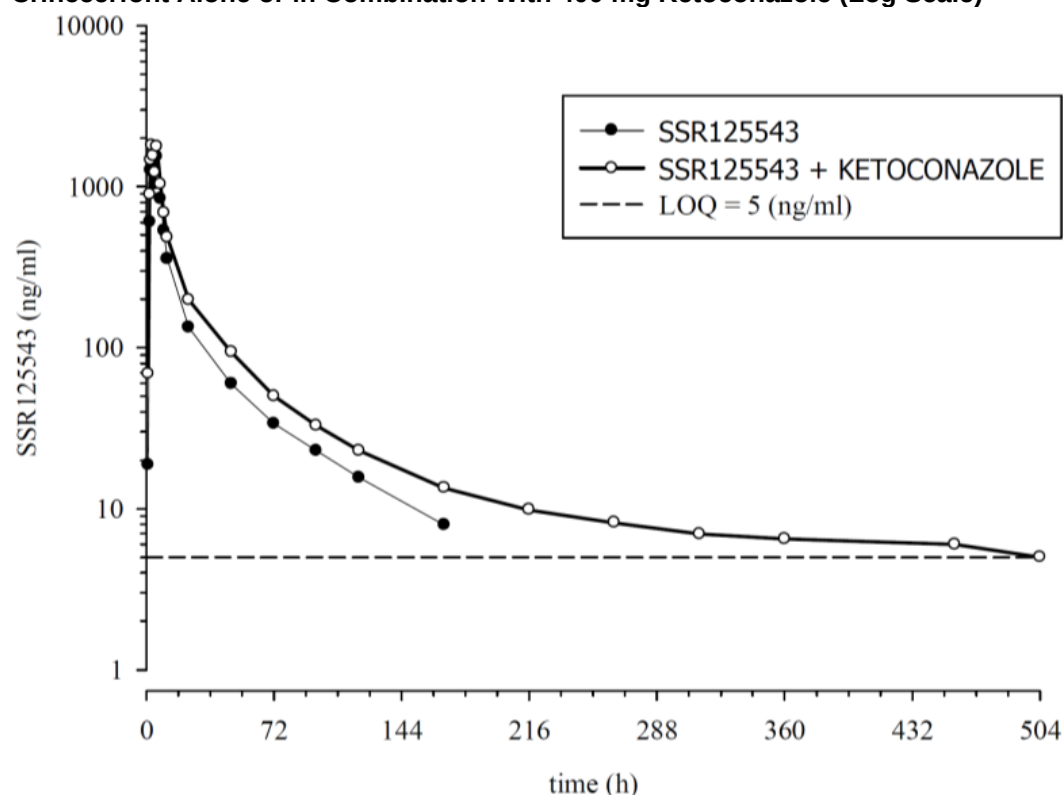
Study Design

This is a phase 1, open-label, two-treatment, single-sequence crossover pharmacokinetic interaction study of 14-day repeated oral 400 mg doses of ketoconazole on the pharmacokinetics of a single oral 50 mg dose of crinecerfont in healthy male subjects. The primary objective of the study was to assess the PK interaction of 14-day repeated oral 400 mg doses of ketoconazole on the pharmacokinetics of crinecerfont following a single oral 50 mg dose in 16 healthy male subjects. In treatment period 1, a single oral dose of 50 mg crinecerfont was administered with a moderate fat breakfast following a 10 hour overnight fast. Following a 22-day washout period, treatment period 2 commenced with subjects receiving 400 mg ketoconazole once daily for 5 days with standardized breakfast. On Day 6 of treatment period 2, subjects received ketoconazole 400 mg and 50 mg crinecerfont with a moderate fat breakfast. Ketoconazole dosing continued from Day 7 to 14 of treatment period 2 with standardized breakfast. PK samples were obtained at prespecified time points over 504 hours for crinecerfont. GMRs with 90% CIs were calculated and compared for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} for crinecerfont with ketoconazole versus reference (crinecerfont alone). All subjects completed the study.

Results

The PK profile of 50 mg crinecerfont with and without ketoconazole 400 mg is presented in [Figure 39](#). Comparison of GMRs with the 90% CIs for $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} for 50 mg crinecerfont with ketoconazole and crinecerfont alone are presented in [Table 148](#).

Figure 39. Mean ($\pm$ SD) Crinecerfont Plasma Concentrations vs. Time for Treatment With 50 mg Crinecerfont Alone or in Combination With 400 mg Ketoconazole (Log Scale)



Source: Figure 3, p.52, Study INT5449. [Link to CSR INT5449](#)
Abbreviations: CSR, clinical study report; LOQ, limit of quantification; SD, standard deviation; SSR125543, crinecerfont

Table 148. PK Exposure Parameters, GMR and 90% CI Comparing 50 mg Crinecerfont With Ketoconazole and 50 mg Crinecerfont Alone

Parameter	Crinecerfont 50 mg	Crinecerfont 50 mg + Ketoconazole 400 mg	GMR (90% CI)
	Geometric Mean (CV%)	Geometric Mean (CV%)	
AUC _{0-tlast} (ng·hr/mL)	17800 (29.0)	25200 (29.0)	1.33 (1.21 to 1.47)
AUC _{0-inf} (ng·hr/mL)	18900 (30.0)	27900 (30.0)	1.45 (1.29 to 1.64)
C _{max} (ng/mL)	1850 (29.0)	2320 (28.0)	1.25 (1.07 to 1.47)

Source: FDA reviewer table from Table 1.1 (Appendix 14.2.5.4.1), p. 539, Table 1.2 (Appendix 14.2.5.4.1), p. 541, and Table 12, p.55, Study INT5449. [Link to CSR INT5449](#)

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-tlast}, AUC from time 0 to the time of the least measurable concentration; AUC_{0-inf}, AUC from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CSR, clinical study report; CV, coefficient of variation; GMR, geometric mean ratio; PK, pharmacokinetic

Conclusions

- Based on the PK analysis, coadministration of crinecerfont with ketoconazole results in an increase in both C_{max} (1.25-fold) and AUC (1.45-fold) as compared to crinecerfont alone.
- Based on the data from this study, crinecerfont metabolism is not significantly impacted with the use of CYP3A4 inhibitors.

20.2.8. Extrinsic Factors: Midazolam Study, Study INT6752

Study Design

This is a phase 1, open-label, two-treatment, single-sequence PK interaction study of 8-day repeated oral 100 mg doses of crinecerfont on single oral doses of midazolam in 15 healthy male subjects.

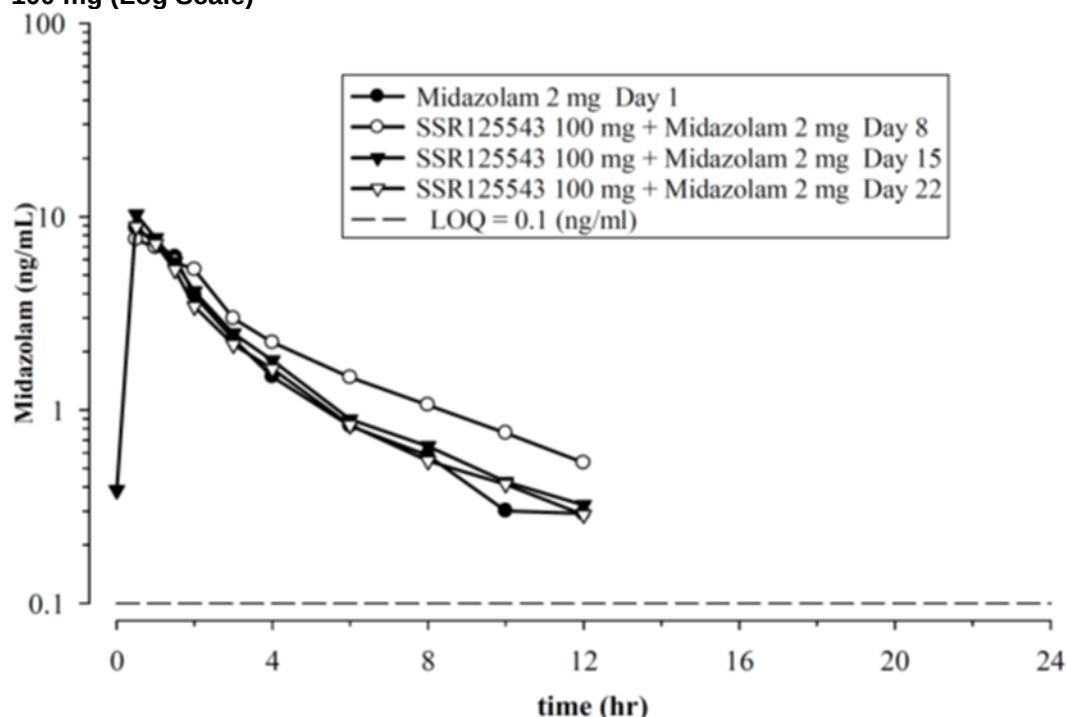
The primary objective of this study is to assess the impact of 8-day repeated oral 100 mg doses of crinecerfont on the pharmacokinetics of midazolam, as a probe substrate for CYP3A activity, and the reversibility of the inhibition of CYP3A activity by crinecerfont 1 and 2 weeks after crinecerfont last administration.

In treatment period 1, a single oral dose of 2 mg midazolam solution was administered under fasting conditions. Following a 48-hour washout period, crinecerfont 100 mg was administered daily with a moderate fat breakfast for 8 days as part of period 2. On Day 8, 15, and 22 of period 2, midazolam 2 mg oral solution was administered. On Day 8 midazolam was administered 2 hours after crinecerfont. PK samples were obtained at prespecified time points over 504 hours for crinecerfont. Midazolam plasma concentrations were obtained for 24 hours postadministration on Day 1 of Period 1, and Days 8, 15, and 22 of Period 2. GMRs with 90% CIs were calculated and compared for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} for midazolam with or post crinecerfont 100 mg dosing versus reference (midazolam alone). All subjects completed the study.

Results

The PK profile of 2 mg midazolam with and without crinecerfont 100 mg is presented in [Figure 40](#). Comparison of GMRs with the 90% CIs for $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} for 2 mg midazolam with or post 100 mg crinecerfont versus midazolam 2 mg alone are presented in [Table 149](#).

Figure 40. Mean ($\pm$ SD) Midazolam 2 mg Plasma Concentration With and Without Crinecerfont 100 mg (Log Scale)



Source: Figure 3, p.61, Study INT6752. [Link to CSR INT6752](#).

Abbreviations: CSR, clinical study report; LOQ, limit of quantification; SD, standard deviation; SSR125543, crinecerfont

Table 149. GMR and 90% CI PK Exposure Parameters of Midazolam Comparing Midazolam 2 mg Administration in Period 2 With (P2D8) and Post (P2D15) 100 mg Crinecerfont Administration as well as Midazolam 2 mg Alone (P1D1)

Comparison	AUC _{0-<i>t</i>last} (ng·hr/mL)		AUC _{0-∞} (ng·hr/mL)		C _{max} (ng/mL)	
	GMR	90% CI	GMR	90% CI	GMR	90% CI
Crinecerfont 100 mg + midazolam 2 mg (P2D8) vs. midazolam 2 mg (P1D1)	1.23	1.09, 1.39	1.23	1.09, 1.38	0.82	0.70, 0.96
Crinecerfont 100 mg + midazolam 2 mg (P2D15) vs. midazolam 2 mg (P1D1)	1.03	0.89, 1.19	1.04	0.89, 1.21	1.02	0.85, 1.22
Crinecerfont 100 mg + midazolam 2 mg (P2D22) vs. midazolam 2 mg (P1D1)	0.95	0.86, 1.05	0.97	0.87, 1.07	0.93	0.78, 1.11

Source: Compiled from Tables 16 - 18, p.65, Study INT6752. [Link to CSR INT6752](#)

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-*t*last}, AUC from time 0 to the time of the least measurable concentration; AUC_{0-∞}, AUC from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CSR, clinical study report; GMR, geometric mean ratio; PK, pharmacokinetic

Conclusions

- Coadministration of midazolam with steady-state concentrations of crinecerfont (8 days) results in a 1.23-fold increase in midazolam AUC, indicating that crinecerfont is a weak inhibitor of CYP3A4.
- Midazolam AUC and $C_{\max}$ levels at 7 days post crinecerfont administration were 1.04- and 1.02-fold, respectively, compared to midazolam treatment alone, thus, indicating reversibility of the CYP3A4 inhibition by crinecerfont.
- While this study was conducted with an earlier formulation of crinecerfont, it is anticipated that the commercial formulation will have a similar impact on the CYP3A enzyme. This is because both formulations are (b) (4). The only difference between the phase 2 and phase 3 capsules (b) (4) in each phase of the study.
- The dose of crinecerfont tested was 100 mg once daily for 8 days prior to midazolam administration. This is not the maximum dose studied in the pivotal phase 3 clinical trial in adults (Trial CAH3003), which was 100 mg twice daily. The study results can still assess the impact of crinecerfont inhibition of CYP3A4. Based on PK data from Trial NBI-74788-CAH2001, crinecerfont exposure in this DDI study may be about 50% lower than that under the maximal clinical dose. Nonetheless, a more than 2-fold increase in midazolam exposure (a minimal effect to be classified as a moderate CYP3A inhibitor) is not expected even if the DDI study had been conducted with 100 mg bid. Overall, crinecerfont is expected to be a weak CYP3A inhibitor at the maximal proposed dose of 100 mg twice daily.

20.2.9. Extrinsic Factors: Oral Contraceptive Steroids Study, Study INT11387

Study Design

This is a phase 1, open-label, non-randomized, single sequence, two-treatment crossover PK interaction of 21-day repeated oral 100 mg doses of crinecerfont on oral contraceptive steroids in healthy female subjects. The primary objective of this study is to assess the effect of 21-day repeated oral doses of 100 mg crinecerfont on the pharmacokinetics of oral contraceptive steroids (OCS) in 25 healthy female subjects. OCS are nonsensitive CYP3A4 substrates, and it is anticipated that a certain portion of the patient population who may be on crinecerfont may also be on OCS. Crinecerfont was shown to be an inhibitor of CYP3A4 in the in vitro studies and, therefore, evaluation of crinecerfont as an inhibitor for CYP3A4 substrates is necessary.

In the run-in phase subjects received an oral Minidril (0.03 mg ethinyl estradiol and 0.15 mg levonorgestrel) tablet alone for 21 days. In treatment period 1, subjects continued with the Minidril oral tablet for an additional 21 days. Following a 7-day washout period, treatment period 2 commenced with subjects receiving Minidril oral tablet with crinecerfont 100 mg for an additional 21 days. OCS were administered with food except during treatment period 2, where both drugs were administered after a moderate fat breakfast. PK samples were obtained at prespecified time points over 24 hours and sparsely for 21 days for crinecerfont and OCS. GMRs with 90% CIs were calculated and compared for $AUC_{0-\infty}$, $AUC_{0-t_{\text{last}}}$, and $C_{\max}$ for ethinyl

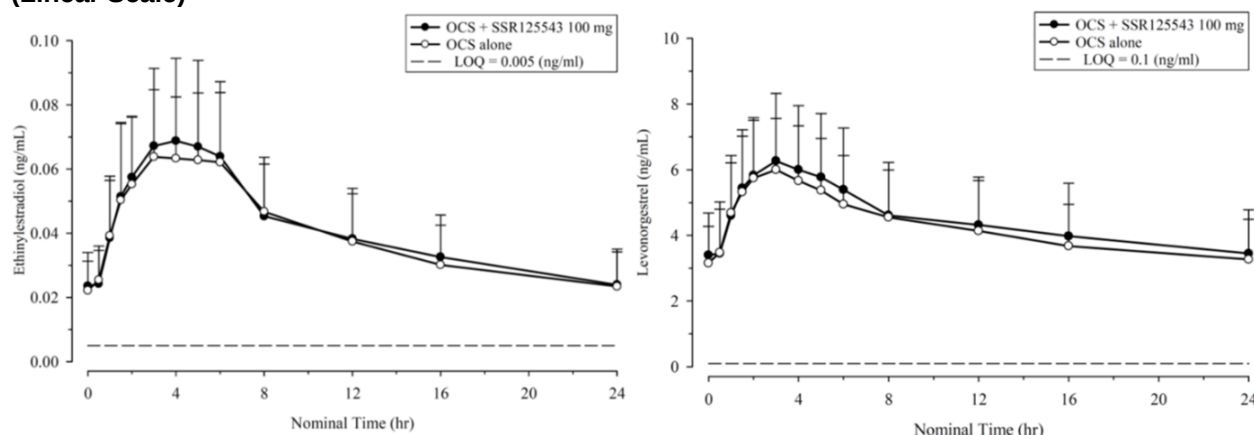
NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

estradiol and levonorgestrel plasma concentrations in OCS with crinecerfont versus reference (OCS alone). All subjects completed the study.

Results

The PK profile of Minidril tablet with and without 100 mg crinecerfont is shown in [Figure 41](#). Comparison of GMRs with the 90% CIs for $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} for Minidril tablet with 100 mg crinecerfont compared to OCS alone are presented in [Table 150](#).

Figure 41. Plasma Concentrations vs. Time for Profiles of Ethinyl Estradiol and Levonorgestrel on Day 21 After Repeated Once Daily Oral Administration of OCS With or Without Crinecerfont (Linear Scale)



Source: Figure 2 (p. 57) and Figure 4 (p.5), Study INT11387. [Link to CSR INT11387](#).

Abbreviations: CSR, clinical study report; LOQ, limit of quantification; OCS, oral contraceptive steroids; SD, standard deviation

Table 150. PK Exposure Parameters, GMR and 90% CI Comparing Plasma Ethinyl Estradiol and Plasma Levonorgestrel Concentrations From OCS When Administered Daily With or Without 100 mg Crinecerfont Over 21 Days

Parameter	Oral Contraceptive (Ethinyl Estradiol 0.03 mg & Levonorgestrel 0.15 mg) Geometric Mean (CV%)		Crinecerfont 100 mg + Oral Contraceptive Geometric Mean (CV%)		GMR (90% CI)	
	EE	LNG	EE	LNG	EE	LNG
$AUC_{0-t_{last}}$ (ng·hr/mL)	0.907 (34)	96.5 (31)	0.931 (36)	101 (34)	1.03 (0.98, 1.08)	1.03 (0.98, 1.12)
C_{max} (ng/mL)	0.0713 (35)	6.46 (25)	0.0758 (32)	6.86 (26)	1.06 (1.01, 1.12)	1.06 (1.01, 1.12)

Source: Compiled from Table 15 (p.61), Table 16 (p.63), Table 17 (p.63), and Table 18 (p. 65) Study INT11387. [Link to CSR INT11387](#)

Crinecerfont PK parameters did not change when dosed with OCS (Data not shown).

Abbreviations: $AUC_{0-t_{last}}$, area under the concentration-time curve from time 0 to the time of the least measurable concentration; CI, confidence interval; C_{max} , maximum observed plasma concentration; CSR, clinical study report; CV, coefficient of variation; GMR, geometric mean ratio; EE, ethinyl estradiol; LNG, levonorgestrel; OCS, oral contraceptive steroids; PK, pharmacokinetic

Conclusions

- The 90% CI values for the GMRs of ethinyl estradiol and levonorgestrel for the Minidril tablet administered over 21-days with or without 100 mg crinecerfont were within bioequivalence criteria of 0.80 to 1.25. At the doses tested there is no interaction between crinecerfont and oral contraceptives containing ethinyl estradiol and levonorgestrel containing oral contraceptives.
- The dose of crinecerfont tested was 100 mg once daily for 21 days with the oral contraceptive. This is not the maximum dose studied in the pivotal phase 3 clinical trial in adults (Trial CAH3003), which was 100 mg twice daily.
- Based on Study INT6752, the review team concluded that crinecerfont is a weak CYP3A inhibitor at clinically relevant doses. Based on FDA Guidance on drug interactions with combined oral contraceptives (COCs) ([June 2023](#)), weak CYP3A inhibitors are unlikely to have a clinically significant increase in COC exposures.

20.2.10. QTc Study, Study NBI-74788-1719

Study Design

This is a phase 1 single-dose, randomized, placebo- and active-controlled, four-way, cross-over study that evaluated the effect of crinecerfont on the QT/QTc (corrected QT) interval in adult healthy subjects. The primary objective of this study was to characterize the effect of a single therapeutic (300 mg) and supratherapeutic (800 mg) dose of crinecerfont on the heart rate- QTc. A total of 48 adult subjects were enrolled and 41 completed the study. Each subject received single doses of crinecerfont 300 mg, crinecerfont 800 mg, placebo, or moxifloxacin 400 mg (positive control).

All treatments were administered with 240 mL water after 30 minutes following the start of a high-fat, high-calorie breakfast. There was a washout period of 21 days between each treatment group. Electrocardiogram samples were collected at specified times for 24 hours postdose. PK samples were obtained at prespecified time points over 504 hours for crinecerfont and placebo groups, while samples were collected at prespecified times for 24 hours for the moxifloxacin group. Crinecerfont and four of its metabolites (NBI-756179, M4, M9, and M11) were analyzed by LC-MS/MS. GMRs were calculated at 300 mg and 800 mg for crinecerfont and its major metabolite NBI-756179.

Results

PK Analysis

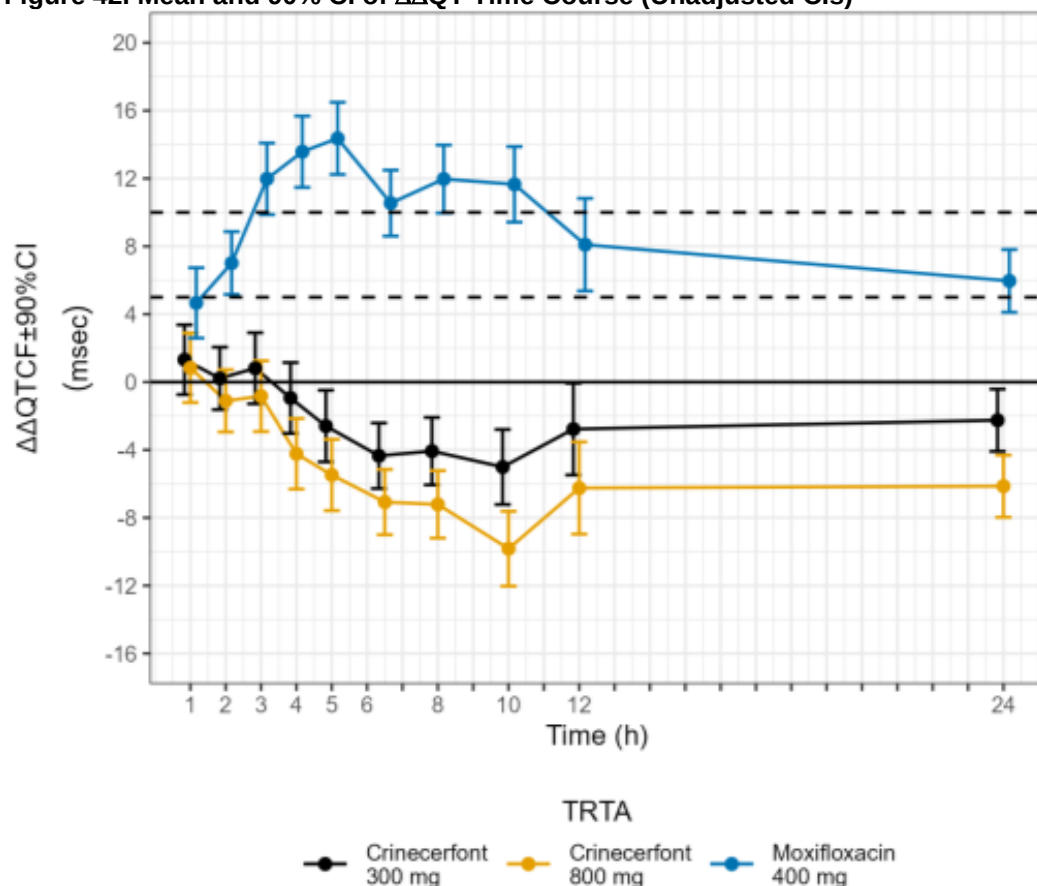
The 800 mg dose of crinecerfont had 2.4-fold high GMRs for $AUC_{0-tlast}$ and $AUC_{0-\infty}$ compared to the 300 mg dose. The 800 mg dose of crinecerfont had a 2.3-fold higher value for C_{max} compared to the 300 mg dose. A similar trend was noted with the major metabolite NBI-756179.

QTc Analysis

The mean-placebo-corrected change in baseline in QT interval corrected for heart rate using Fridericia's correction ($\Delta\Delta QTcF$) and 90% CI following 300 mg crinecerfont, 800 mg

crinecerfont, and 400 mg moxifloxacin are presented in [Figure 42](#). At a 1 hour the $\Delta\Delta QT_c$ for the 800 mg crinecerfont dose was +1.61 msec. At 2 hours post-300 mg and 800 mg doses of crinecerfont until 24 hours postdose, the $\Delta\Delta QT_c$ values were negative. For further details please see the review by the QTc-IRT (interdisciplinary review team) dated August 21, 2024.²⁹

Figure 42. Mean and 90% CI of $\Delta\Delta QT$ Time Course (Unadjusted CIs)



Source: FDA Analysis. Figure 2, p. 8, QT/IRT Report. DARRTS, reference ID 5430486
Abbreviations: CI, confidence interval; TRTA, treatment arms

Conclusions

Per review from the Interdisciplinary Review Team for Cardiac Safety Studies:³⁰

- Crinecerfont did not prolong the QT_c interval in this thorough QT study. Instead, crinecerfont shortened the QT_c interval in a dose-dependent manner. The highest dose in the thorough QT study provides 3.3-fold the high clinical C_{max} .
- The small magnitude of QT_c shortening at high clinical exposure (-5 msec) in the thorough QT study is unlikely to be clinically important.
- Labeling recommendation: (b) (4)

²⁹ DARRTS, reference ID 5430486

³⁰ DARRTS, reference ID 5430486

20.2.11. Pilot Ensure Plus Study, Study NBI-74788-1601

Study Design

This is a phase 1, randomized, open-label, two-period crossover study to evaluate the pharmacokinetics, the effect of food on the pharmacokinetics, and safety of crinecerfont (NBI-74788) in healthy adult subjects. A total of 16 subjects were randomized to receive NBI-74788 (crinecerfont) under fasted or fed conditions. Following a washout period of 21 days, subjects crossed over into the alternate group. Subjects in the fasted group, fasted overnight for at least 10 hours and continued to fast an additional 4 hours postdrug administration. Subjects in the fed group also fasted for at least 10 hours overnight and had liquid supplement breakfast with the study drug. Study intervention was an oral 50 mg crinecerfont (b) (4) formulation that was consumed with 240 mL water (fasted state) or Ensure Plus (350 calories; fed state). PK samples were obtained at prespecified time points over 504 hours and GMRs with 90% CIs were calculated and compared for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} under fed and fasted conditions.

Results

Comparison of GMRs with the 90% CIs for $AUC_{0-t_{last}}$ and C_{max} for 50 mg crinecerfont are presented in [Table 151](#). Missing values precluded the calculation of $AUC_{0-\infty}$ GMR and 90% CI.

Table 151. Crinecerfont GMR and 90% CI for PK Parameters Under Fed and Fasted Conditions

Parameter	Ratio ^a (%) (Fed vs. Fasted Condition)	90% Confidence Interval ^b
$AUC_{0-t_{last}}$ (ng·hr/mL)	215.2	182.9, 253.1
C_{max} (ng/mL)	218.6	187.4, 255.1

Source: Table 5, page 34, Study NBI-74788-1601. [Link to 1601 CSR](#)

^a Ratio of geometric least-squares means was based on a mixed model using log-transformed (base 10) data.

^b The 90% confidence interval for geometric mean ratio was based on least-squares means using log-transformed (base 10) data.

Abbreviations: $AUC_{0-t_{last}}$, area under the concentration-time curve from time 0 to the time of the least measurable concentration; CI, confidence interval; C_{max} , maximum observed plasma concentration; CSR, clinical study report; GMR, geometric mean ratio; PK, pharmacokinetic

Conclusions

Comparison of GMRs with the 90% CIs for $AUC_{0-t_{last}}$ and C_{max} indicates that food increases the absorption of crinecerfont by approximately 2-fold.

20.2.12. Pilot Formulation Study, Study NBI-74788-1704

Study Design

This is a phase 1, randomized, open-label, three-period crossover study to evaluate the relative bioavailability, effect of food on pharmacokinetics, and safety of crinecerfont (NBI-74788) formulations in healthy adult subjects. Study objectives were to evaluate the pharmacokinetics, compare the relative bioavailability, effect of food, safety, and tolerability of crinecerfont 50 mg formulations. A total of 36 subject were randomized into four treatment sequences across three

treatment periods where subjects received (b) (4) formulation (reference capsule; fed state only), (b) (4) capsule or (b) (4) suspension formulation under fed conditions and (b) (4) capsule or (b) (4) suspension under fasted conditions.

A washout period of 21 days was included between treatment periods. Subjects in the fasted group fasted overnight for at least 10 hours and continued to fast an additional 4 hours postdrug administration. Subjects in the fed group also fasted for at least 10 hours overnight and had liquid supplement breakfast with the study drug. Study interventions, 50 mg reference capsule, 50 mg (b) (4) capsule, and 50 mg (b) (4) suspension, were consumed with water 240 mL (fasted state) or Ensure Plus (350 calories; fed state). The 50 mg (b) (4) capsule was consumed with an additional 100 mL water, while the (b) (4) suspension contributed an additional 80 mL of liquid. PK samples were obtained at prespecified time points over 504 hours and GMRs with 90% CIs were calculated and compared for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} for the (b) (4) capsule or (b) (4) suspension compared to reference under fed and fasted conditions.

Results

GMRs with the 90% CIs for $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} for 50 mg crinecerfont in the different formulations are presented in [Table 152](#).

Table 152. Crinecerfont GMRs and 90% CI PK Exposure Parameters Comparing the (b) (4) Capsule and (b) (4) Suspension to Reference Formulation Under Fasted and Fed Conditions

Treatment Comparison	$AUC_{0-t_{last}}$ (ng·hr/mL)		$AUC_{0-\infty}$ (ng·hr/mL)		C_{max} (ng/mL)	
	GMR (%)	90% CI	GMR (%)	90% CI	GMR (%)	90% CI
(b) (4) capsule (fed) vs. reference capsule (fed)	0.48	0.41, 0.56	0.50	0.43, 0.57	0.60	0.52, 0.69
(b) (4) capsule (fasted) vs. reference capsule (fed)	0.08	0.06, 0.11	0.09	0.07, 0.12	0.07	0.05, 0.09
(b) (4) suspension (fed) vs. reference capsule (fed)	0.32	0.26, 0.39	0.34	0.28, 0.41	0.42	0.35, 0.51
(b) (4) suspension (fasted) vs. reference capsule (fed)	0.04	0.03, 0.06	0.05	0.04, 0.07	0.05	0.04, 0.05

Source: Compiled from Table 5, page 37, and Table 8, page 42 Study NBI-74788-1704. [Link to CSR 1704](#)

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-t_{last}}$, AUC from time 0 to the time of the least measurable concentration; $AUC_{0-\infty}$, AUC from time 0 to infinity; CI, confidence interval; C_{max} , maximum observed plasma concentration; CSR, clinical study report; GMR, geometric mean ratio; PK, pharmacokinetic; (b) (4)

Conclusions

- The (b) (4) capsule formulation in the fed and fasted state compared to the reference capsule in the fed state had approximately 2-fold and 8-fold lower exposure, respectively.
- The (b) (4) Suspension formulation in the fed and fasted state compared to the reference formulation in the fed state had approximately 3-fold and 22-fold lower exposure, respectively.
- Overall, the reference (b) (4) formulation had better relative bioavailability and greater absorption compared to the two (b) (4) formulations.

20.2.13. Capsule Food-Effect Study, Study NBI-74788-1712

Study Design

This is a phase 1, randomized, open-label, four-period crossover study to evaluate the effect of food with different levels of fat and caloric content on the pharmacokinetics and safety of crinecerfont in healthy adult subjects. Study objectives were to evaluate the pharmacokinetics, effect of food with different levels of fat and caloric content, and safety and tolerability of crinecerfont 100 mg crinecerfont capsules ((b) (4) formulation). A total of 16 subjects were randomized into one of four treatment groups to receive 100 mg of crinecerfont capsules with the reference meal or test meals 1–3 with a washout period of 21 days between each dose. The particulars of the meals are provided in [Table 153](#).

Table 153. Meal Composition, Food-Effect Study NBI-74788-1712

Meals	Type	Meal Composition	Time to Consume Study (min) Intervention
Reference (liquid dietary supplement)	8 oz vanilla-flavored Ensure Plus	350 calories, 11 grams total fat, 20 grams sugars, 13 grams protein, and 50 grams carbohydrate	2 2 x 50 mg capsules +120 mL water
Test meal 1 (low-fat, low caloric meal)	4 oz Ensure vanilla pudding	170 calories, 5 grams total fat, 15 grams sugars, 4 grams protein, and 30 grams total carbohydrates	2 2 x 50 mg capsules +120 mL water
Test meal 2 (low-fat, low caloric meal)	8 oz glass of whole milk	149 calories, 7.9 grams total fat, 12 grams sugars, 7.7 grams protein, and 12 grams total carbohydrates	2 2 x 50 mg capsules +120 mL water
Test meal 3 (high-fat, high-caloric meal)	2 slices of buttered toast, 2 eggs fried in butter, 2 strips of bacon, 4 oz of hash brown potatoes, and 240 mL of whole milk	~800 to 1000 calories, of which ~50 to 60% is derived from fat	30 2 x 50 mg capsules +120 mL water

Source: Section 9.4.1, p18, Study NBI-74788-1712. [Link to CSR 1712](#)

PK samples were obtained at prespecified time points over 504 hours and GMRs with 90% CIs were calculated and compared for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} in the test meal groups to the reference meal group for 100 mg crinecerfont.

Results

GMRs with the 90% CIs for $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} for 100 mg crinecerfont in the different formulations are presented in [Table 154](#).

Table 154. Crinecerfont 100 mg Dose GMRs and 90% CI PK Exposure Parameters Comparing Test Meals (1–3) Compared to Reference Meal

Food-Effect Comparison	$AUC_{0-t_{last}}$ (ng·hr/mL)		$AUC_{0-\infty}$ (ng·hr/mL)		C_{max} (ng/mL)	
	GMR	90% CI	GMR	90% CI	GMR	90% CI
Test meal 1 vs. reference meal	0.98	0.84, 1.14	1.01	0.89, 1.14	1.01	0.81, 1.26
Test meal 2 vs. reference meal	0.99	0.87, 1.12	0.98	0.87, 1.10	0.94	0.76, 1.15
Test meal 3 vs. reference meal	1.53	1.40, 1.68	1.49	1.37, 1.62	1.35	1.14, 1.60

Source: Compiled from Table 6, page 38, Study NBI-74788-1712. [Link to CSR 1712](#)

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-t_{last}}$, AUC from time 0 to the time of the least measurable concentration; $AUC_{0-\infty}$, AUC from time 0 to infinity; CI, confidence interval; C_{max} , maximum observed plasma concentration; CSR, clinical study report; GMR, geometric mean ratio; PK, pharmacokinetic

Conclusions

- Low fat, low caloric meals (test meal 1 and test meal 2) resulted in similar PK exposure, in terms of AUC and C_{max} to the reference meal. The 90% CI for the GMRs were within the bioequivalence range of 80 to 125%.
- High-fat, high-caloric meal (test meal 3) increased the PK exposure (AUC and C_{max}) of crinecerfont by ~50% compared to the low-fat, low calorie reference meal.

20.2.14. Oral Solution Bioavailability vs. Capsule Bioavailability, Study NBI-74788-1716

Study Design

This is a phase 1, open-label study to evaluate the pharmacokinetics, relative bioavailability, effect of food, safety, and tolerability of different crinecerfont prototype formulations in healthy adult subjects. The primary study objective was to determine the relative oral bioavailability of three prototype formulations, two (b) (4) and one (b) (4), as compared to the oral reference capsule for crinecerfont. The formulations, doses and study conditions are outlined in [Table 155](#) and [Figure 43](#). A total of 36 subjects were enrolled in the study and the number that completed the study for each regimen are included in [Table 155](#). Four subjects withdrew from the study; one had a treatment-emergent adverse event (TEAE) of increased AST levels after the 100 mg dose of prototype formulation 1 (regimen E), two withdrew consent, and one had poor venous access.

As part of the crossover design, a washout period between formulations of 14 days (between periods 1 and 2) or 21 days (between periods 2 and 3, and 3 and 4) was allotted ([Figure 43](#)). The 21-day washout period accommodated interim data reviews. PK samples were obtained at prespecified time points over 36 hours and GMRs with 90% CIs were calculated and compared for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$ and C_{max} in the test groups (regimens B, C, and D) to the reference

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

capsule group (regimen A). For the food effect, GMRs with 90% CIs were calculated and compared for $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} comparing regimen F (alternate diet; Angel Delight™) and regimen D (Ensure Plus).

Table 155. Formulation, Dosing Regimen, Prandial State, and Number of Subjects, Study NBI-74788-1716

Formulation	Regimen	Dose (mg)	Prandial State	Number of Subjects Who Completed the Regimen
50 mg capsules (reference)	A	50 mg	Fed (Ensure Plus) ^b	35
Oral solution, prototype formulation 1 (PF1), 50 mg/mL	B	50 mg	Fed (Ensure Plus)	12
(b) (4)	E	100 mg		16
Oral solution, PF 2, 50 mg/mL	C	50 mg	Fed (Ensure Plus)	12
(b) (4)				
Granule for sprinkle	D	50 mg	Fed (Ensure Plus)	12
	F		Fed (Angel Delight) ^c	15

Source: Compiled from synopsis and clinical study report section 9 Study Subjects p. 18–21, and Table 6, p. 31. [Link to Synopsis 1716](#) and [Link to CSR 1716](#).

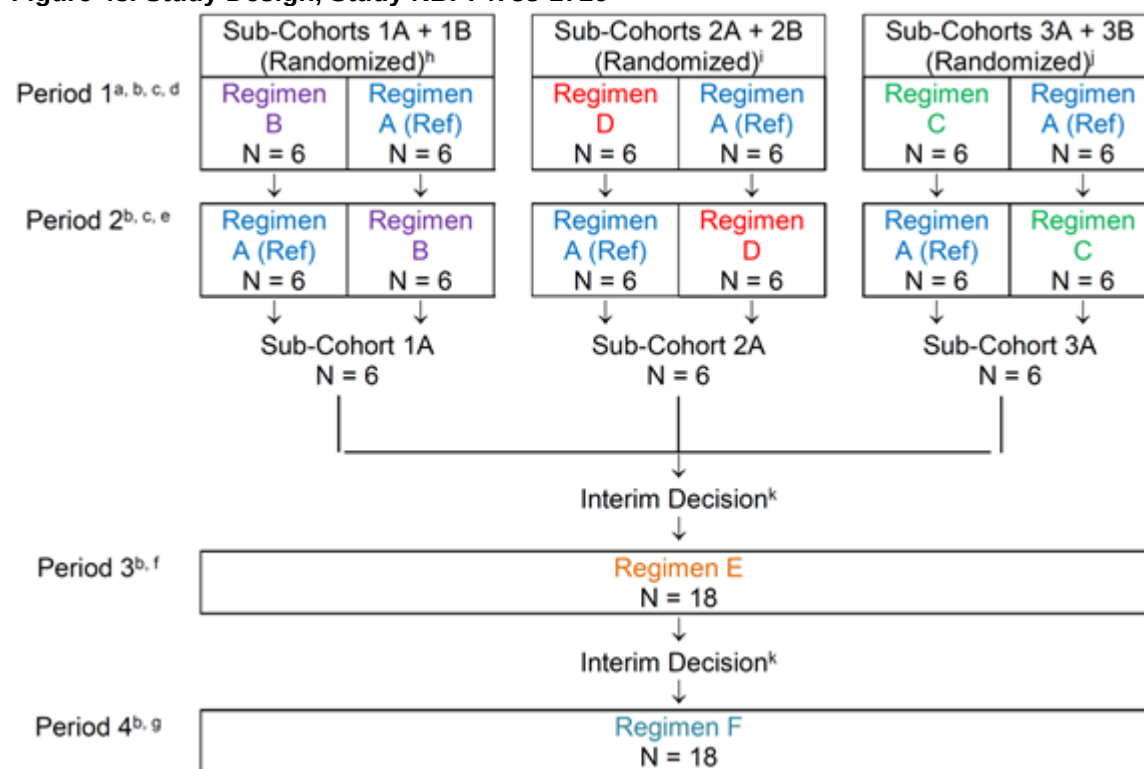
^a PF2 is the oral solution formulation used in the phase 3 study and is the final marketed formulation proposed by the Applicant

^b Ensure Plus (100 mL): 150 calories, 4.92 g fat, 20.2 g carbohydrate, 0 g fiber, and 6.25 g protein

^c Angel Delight (100 g): 119 calories, 3.6 g fat, 17.8 g carbohydrate, 0.6 g fiber, and 3.6 g protein

Abbreviations: CSR, clinical study report

Figure 43. Study Design, Study NBI-74788-1716



Source: Figure 1, page 20, Study NBI-74788-1716. [Link to CSR 1716](#).

Abbreviations: CSR, clinical study report; ref, reference

Results

GMRs with the 90% CIs for $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} for 50 mg crinecerfont in the different formulations are presented in [Table 156](#).

Table 156. Crinecerfont 50 mg Dose GMR and 90% CI PK Exposure Parameters Comparing Regimens B, C, or D to the Reference Capsule (Regimen A)

Formulation Comparison	$AUC_{0-t_{last}}$ (ng·hr/mL)		$AUC_{0-\infty}$ (ng·hr/mL)		C_{max} (ng/mL)	
	GMR (%)	90% CI	GMR (%)	90% CI	GMR (%)	90% CI
Regimen B (PF1) vs. regimen A (n=11)	0.43	0.34, 0.54	0.46	0.36, 0.57	0.53	0.43, 0.65
Regimen C (PF2) ^a vs. regimen A (n=11)	0.85	0.68, 1.06	0.87	0.71, 1.07	0.83	0.67, 1.02
Regimen D (granule) vs. regimen A (n=12)	0.64	0.50, 0.83	0.65	0.50, 0.83	0.84	0.67, 1.06

Source: Compiled from Table 14.2.3.1, p.170, Study NBI-74788-1716. [Link to CSR 1716](#).

^a Regimen C is the oral formulation used in the phase 3 study

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-t_{last}}$, AUC from time 0 to the time of the least measurable concentration; $AUC_{0-\infty}$, AUC from time 0 to infinity; CI, confidence interval; C_{max} , maximum observed plasma concentration; CSR, clinical study report; GMR, geometric mean ratio; n, number of subjects evaluated in comparison; PF, prototype formulation; PK, pharmacokinetic

Conclusions

Relative to the reference treatment (regimen A: 50 mg crinecerfont capsule administered with Ensure Plus), the liquid formulation (prototype formulation 2; regimen C: clinical and commercial oral solution formulation administered with Ensure Plus) had C_{max} , $AUC_{0-t_{last}}$, and $AUC_{0-\infty}$ values ~15% lower with 90% CI outside the 80–125% range needed to be considered bioequivalent to the reference formulation. However, given that the sample size is only 12 subjects, this may not reflect the true bioequivalence (BE) assessment.

It should be noted that the phase 2 capsule formulation used in this Study is nearly identical in composition to the phase 3 capsule formulation used in the pivotal clinical trials, Trial CAH2006 (pediatric study) and Trial CAH3003 (adult study). The only difference is (b) (4)

(Reference Module 2.3.P Drug Product).

Data from regimens B and D are not relevant to this submission and will not be discussed.

20.2.15. Oral Solution Food-Effect Study and Dose Linearity From 25 mg to 100 mg, Study NBI-74788-1734

Study Design

This is a phase 1, randomized, open-label study in healthy adult subjects to evaluate the effect of food on the bioavailability of 100 mg crinecerfont oral solution and to estimate the bioavailability of 25 mg and 50 mg crinecerfont oral solution relative to 100 mg crinecerfont oral solution. A total of 16 healthy adult subjects between 19 and 55 years of age were enrolled and 15 completed the study. One subject dropped out due to COVID. Crinecerfont oral solution at 25 mg, 50 mg, and 100 mg under fed conditions and 100 mg under fasted conditions were

administered to the subjects in a cross-over design with a washout period of 21 days. All subjects fasted overnight for at least 10 hours. For subjects in the fed state, a high-fat, high-calorie meal was consumed in 30 minutes and was followed by drug administration. For subjects in the fasted state, drug was administered with 240 mL of water. PK samples were obtained at prespecified time points over 504 hours. Statistical Analysis for the food-effect and dose proportionality include calculation of GMRs with 90% CIs and comparing $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} . Analysis of dose proportionality was based on dose-normalized $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} . Three subjects were excluded from the PK analysis due to vomiting (subject (b) (6)), and predose crinecerfont plasma concentrations greater than 5% of the crinecerfont C_{max} (subjects (b) (6) and (b) (6)).

Results

GMRs with the 90% CIs for $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} for 100 mg crinecerfont under fed and fasted conditions are presented in Table 157. To assess dose proportionality, dose-normalized $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} for 25 mg, 50 mg, and 100 mg crinecerfont under fed conditions were analyzed and are presented in Table 158.

Table 157. Crinecerfont 100 mg Oral Solution GMR and 90% CI PK Exposure Parameters Comparing Food Effect

Food Effect at 100 mg	AUC _{0-t_{last}} (ng·hr/mL)		AUC _{0-∞} (ng·hr/mL)		C _{max} (ng/mL)	
	GMR	90% CI	GMR	90% CI	GMR	90% CI
Crinecerfont 100 mg fed vs. crinecerfont 100 mg fasted	8.16	6.49, 10.3	8.27	6.22, 11.0	8.57	6.84, 10.7

Source: Table 7, p. 29, Study NBI-74788-1734. [Link to CSR 1734](#).

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-t_{last}}$, AUC from time 0 to the time of the least measurable concentration; $AUC_{0-\infty}$, AUC from time 0 to infinity; CI, confidence interval; C_{max} , maximum observed plasma concentration; CSR, clinical study report; GMR, geometric mean ratio; PK, pharmacokinetic

Table 158. Crinecerfont 25 to 100 mg Dose Proportionality Analysis

Evaluated Dose Range	Dose-Normalized AUC _{0-t_{last}} ((ng·hr/mL)/mg)				Dose-Normalized AUC _{0-∞} ((ng·hr/mL)/mg)			Dose-Normalized C _{max} ((ng/mL)/mg)		
	Slope	90% CI	p-Value		Slope	90% CI	p-Value	Slope	90% CI	p-Value
25-100 mg	-0.05	-0.20, 0.11	0.6264		-0.08	-0.24, 0.08	0.4244	0.11	-0.12, 0.33	0.4180

Source: Table 6, p. 28, Study NBI-74788-1734. [Link to CSR 1734](#)

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-t_{last}}$, AUC from time 0 to the time of the least measurable concentration; $AUC_{0-\infty}$, AUC from time 0 to infinity; CI, confidence interval; C_{max} , maximum observed plasma concentration; CSR, clinical study report

Conclusions

- Following a high-fat, high-calorie meal, crinecerfont 100 mg oral solution drug exposure increased by approximately 8-fold compared to the same dose under fasted conditions.
- Dose proportionality analysis demonstrates that the oral solution is dose-proportional between 25 to 100 mg.

20.2.16. Phase 3 Hard Gel Capsule vs. Commercial Soft Gel Capsule Bioavailability and Food Effect for Commercial Soft Gel Capsule, Study NBI-74788-1736

Study Design

This is a phase 1, randomized, open-label study in healthy adult subjects to evaluate the bioequivalence of soft gel and hard gel crinecerfont capsules and the effect of food on bioavailability. The primary objectives of this study are to determine the BE under fed conditions, of 100 mg crinecerfont soft gel capsule (commercial formulation) relative to 2×crinecerfont 50 mg hard gel capsules (phase 3 capsules); additionally, this study also evaluated the effect of food on the pharmacokinetics of 100 mg crinecerfont soft gel formulation (commercial formulation). A total of 50 adult subjects were enrolled and 44 subjects completed the study. A total of 49 subjects contributed to the BE study, while a subset of 19 subjects were used for the food-effect evaluation of the commercial formulation. For the BE study, crinecerfont 2×50 mg hard gel capsules, or 1×100 mg soft gel capsule under fed conditions were administered to the subjects in a cross-over design with a washout period of 21 days.

For the food-effect study for the commercial capsules, data were reviewed from the BE study and 19 subjects were recruited for the study and received 1×100 mg soft gel capsule under fasted conditions. All subjects fasted overnight for at least 10 hours. For subjects in the fed state, a high-fat, high-calorie meal was consumed in 30 minutes and was followed by drug administration. For subjects in the fasted state, drug was administered with 240 mL of water. PK samples were obtained at prespecified time points over 504 hours. Statistical analysis for the BE between the phase 3 capsule and the commercial capsule food effect for the commercial capsule included calculation of GMRs with 90% CIs comparing $AUC_{0-\infty}$, $AUC_{0-t_{last}}$, and C_{max} .

Results

GMRs with the 90% CIs for $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} for 100 mg crinecerfont hard gel and soft gel capsules are presented in [Table 159](#). Comparison of GMRs with the 90% CIs for $AUC_{0-t_{last}}$, $AUC_{0-\infty}$, and C_{max} for 100 mg crinecerfont soft gel capsules under fasted and fed conditions are presented in [Table 160](#). These results were independently confirmed by reviewer analysis.

Table 159. Crinecerfont 100 mg Hard Gel Capsule (Phase 3 Capsule) and the Soft Gel Capsule (Commercial Formulation) GMR and 90% CI PK Exposure Parameters

Bioequivalence Between Phase 3 Capsule and Commercial Capsule	$AUC_{0-t_{last}}$ (ng·hr/mL)		$AUC_{0-\infty}$ (ng·hr/mL)		C_{max} (ng/mL)	
	GMR	90% CI	GMR	90% CI	GMR	90% CI
Crinecerfont 100 mg fed vs. crinecerfont 100 mg fasted	1.01	0.94, 1.09	0.99	0.91, 1.08	1.07	0.98, 1.16

Source: Table 10, p. 48, Study NBI-74788-1736. [Link to CSR 1736](#)

Abbreviations: AUC, area under the concentration-time curve; $AUC_{0-t_{last}}$, AUC from time 0 to the time of the least measurable concentration; $AUC_{0-\infty}$, AUC from time 0 to infinity; CI, confidence interval; C_{max} , maximum observed plasma concentration; CSR, clinical study report; GMR, geometric mean ratio; PK, pharmacokinetic

Table 160. Crinecerfont 100 mg Soft Gel Capsule (Commercial Formulation) GMR and 90% CI PK Exposure Parameters Comparing Food Effect

Food Effect at 100 mg for Commercial Capsules	AUC _{0-tlast} (ng·hr/mL)		AUC _{0-∞} (ng·hr/mL)		C _{max} (ng/mL)	
	GMR (%)	90% CI	GMR (%)	90% CI	GMR (%)	90% CI
Crinecerfont 100 mg fed vs. Crinecerfont 100 mg fasted	3.78	3.37, 4.25	3.27	2.87, 3.73	4.95	4.09, 5.98

Source: Table 12, p. 59, Study NBI-74788-1736. [Link to CSR 1736](#)

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-tlast}, AUC from time 0 to the time of the least measurable concentration; AUC_{0-∞}, AUC from time 0 to infinity; CI, confidence interval; C_{max}, maximum observed plasma concentration; CSR, clinical study report; GMR, geometric mean ratio; PK, pharmacokinetic

Conclusions

- Bioequivalence was demonstrated between the phase 3 capsule (hard gel) and the commercial capsule, at the 100 mg dose level, as the 90% CI values for GMR for AUC and C_{max} were within the specified criteria of 0.8–1.25.
- Following a high-fat, high-calorie meal, crinecerfont 100 mg oral soft gel capsule dose exposure increased between 3 to 4-fold compared to the same dose under fasted conditions.

20.2.17. Phase 2 Dose-Finding Study, Trial NBI-74788-CAH2001

Study Design

This is a phase 2, open-label, multiple-dose, dose-escalation study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of crinecerfont in adult female and male subjects (18 to 50 years of age) with a documented medical diagnosis of classic CAH with a serum 17-OHP level of $\geq 1,000$ ng/dL at screening. The primary objectives of this study are to assess different dosing regimens of crinecerfont in adults with CAH, evaluate the effect of repeated doses of crinecerfont and different dosing regimens on endogenous levels of pharmacodynamic (PD) biomarkers in adults with CAH, and evaluate the plasma exposures following repeated doses of crinecerfont.

Crinecerfont doses evaluated were:

- Cohort 1: 50 mg once daily at bedtime (2200 hours) (n=8 enrolled/8 completed)
- Cohort 2: 100 mg once daily at bedtime (2200 hours) (n=7 enrolled/6 completed)
- Cohort 3: 100 mg once daily with evening meal (1900 hours) (n=8 enrolled/7 completed)
- Cohort 4: 100 mg twice daily with breakfast (0700 hours) and evening meal (1900 hours) (n=8 enrolled/8 completed)

Each dosing regimen was administered over 14 consecutive days. A total of 18 subjects were enrolled in the study, of which 13 subjects were re-enrolled in cohorts 3 and 4. Cohorts 1 and 2 received the crinecerfont dose with 237 mL of vanilla-flavored Ensure Plus while subjects in cohorts 3 and 4 were in outpatient settings for most of the study duration and ate meals at home. On the last day of dosing, subjects took the drug in cohorts 3 and 4 following a moderate fat, moderate calorie evening meal. All subjects took their usual morning dose of concurrent steroidal treatments at approximately 1000 hours.

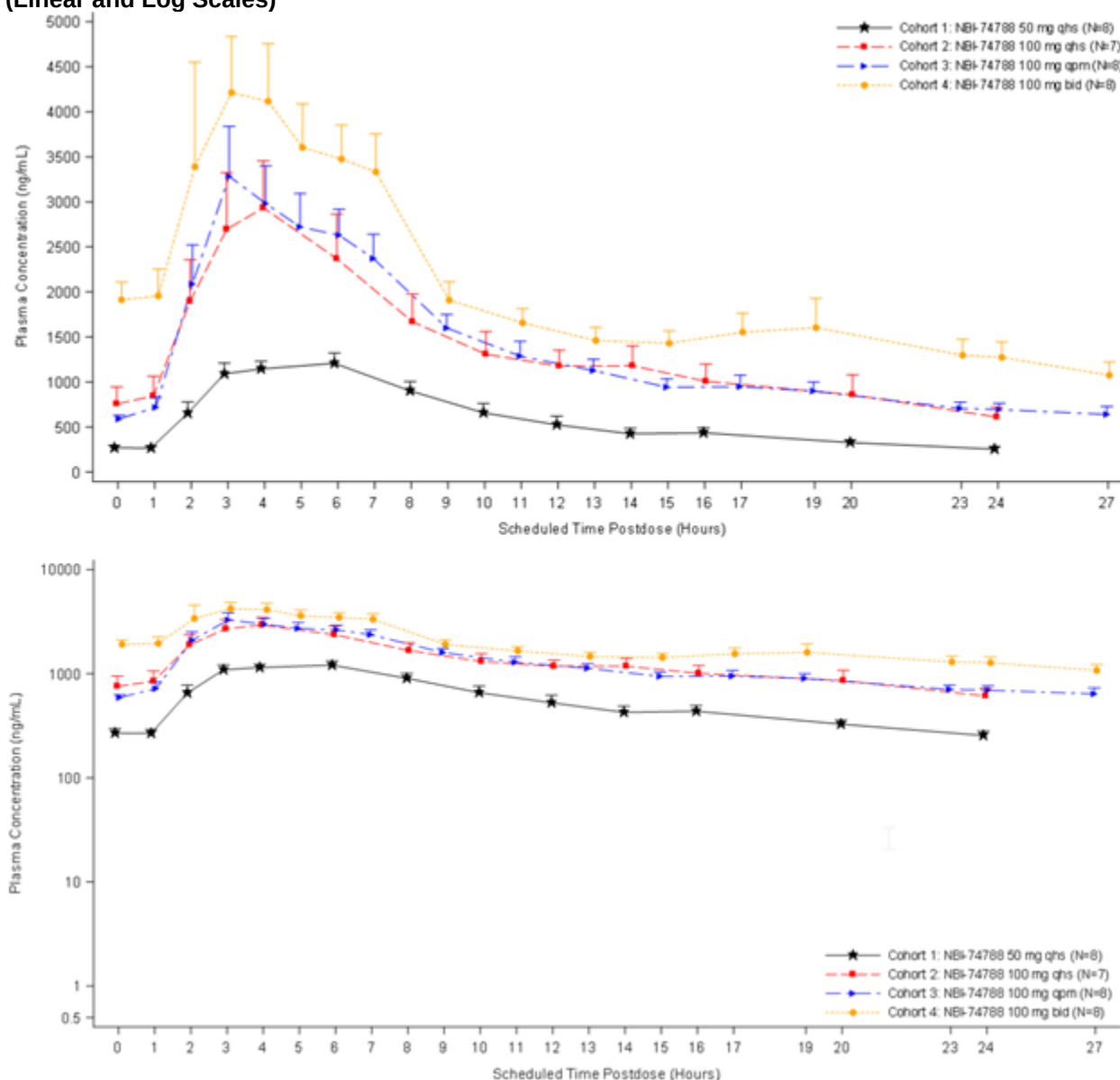
NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

PK samples were obtained at prespecified time points over 504 hours and plasma PK parameters were calculated for crinecerfont and metabolite NBI-756179. Primary PD samples (17-OHP) were obtained at screening and postdose at prespecified times over 15 hours. Key secondary PD samples were obtained over 24 hours to determine average 17-OHP, A4, and ACTH over 24 hours.

Results

The mean crinecerfont plasma concentration versus time profile for the four cohorts is presented in [Figure 44](#) and the summary of PK parameters for the four cohorts is presented in [Table 161](#).

Figure 44. Mean ($\pm$ SD) Crinecerfont Plasma Concentrations vs. Time on Day 14 for Cohorts 1 to 4 (Linear and Log Scales)



Source: Figure 5, p. 59, Study NBI-74788-2001. [Link to CSR 2001](#)

Abbreviations: bid, twice daily; CSR, clinical study report; qhs, once a day at bedtime; qpm, every evening; SD, standard deviation

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

Table 161. Summary of Crinecerfont Plasma PK Parameters on Day 14 by Cohort

Parameter Statistic	Cohort 1: 50 mg qhs (N=8)	Cohort 2: 100 mg qhs (N=7)	Cohort 3: 100 mg qpm (N=8)	Cohort 4: 100 mg bid (N=8)
AUC ₂₄ (ng·hr/mL)				
Mean (SD)	14300 (3480)	37400 (14100)	34800 (6300)	66900 (20200)
CV(%)	24.2	37.7	18.1	30.2
C _{max} (ng/mL)				
Mean (SD)	1350 (205)	3510 (1090)	3810 (1200)	5590 (2760)
CV (%)	15.2	31.0	31.6	49.3
T _{max} (hours)				
Median (min, max)	4.0 (3.0, 6.0)	4.0 (3.0, 4.0)	3.0 (2.0, 7.0)	4.0 (2.0, 7.0)
C _{ave} (ng/mL)				
Mean (SD)	598 (145)	1560 (587)	1450 (262)	2790 (841)
CV (%)	24.2	37.7	18.1	30.2
Fluctuation (%)				
Mean (SD)	190 (33)	190 (30)	230 (93)	140 (44)
CV (%)	18	16	41	39
CL/F (L/hr)				
Mean (SD)	3.7 (0.92)	3.0 (1.0)	2.9 (0.43)	3.2 (0.92)
CV (%)	25	34	15	29

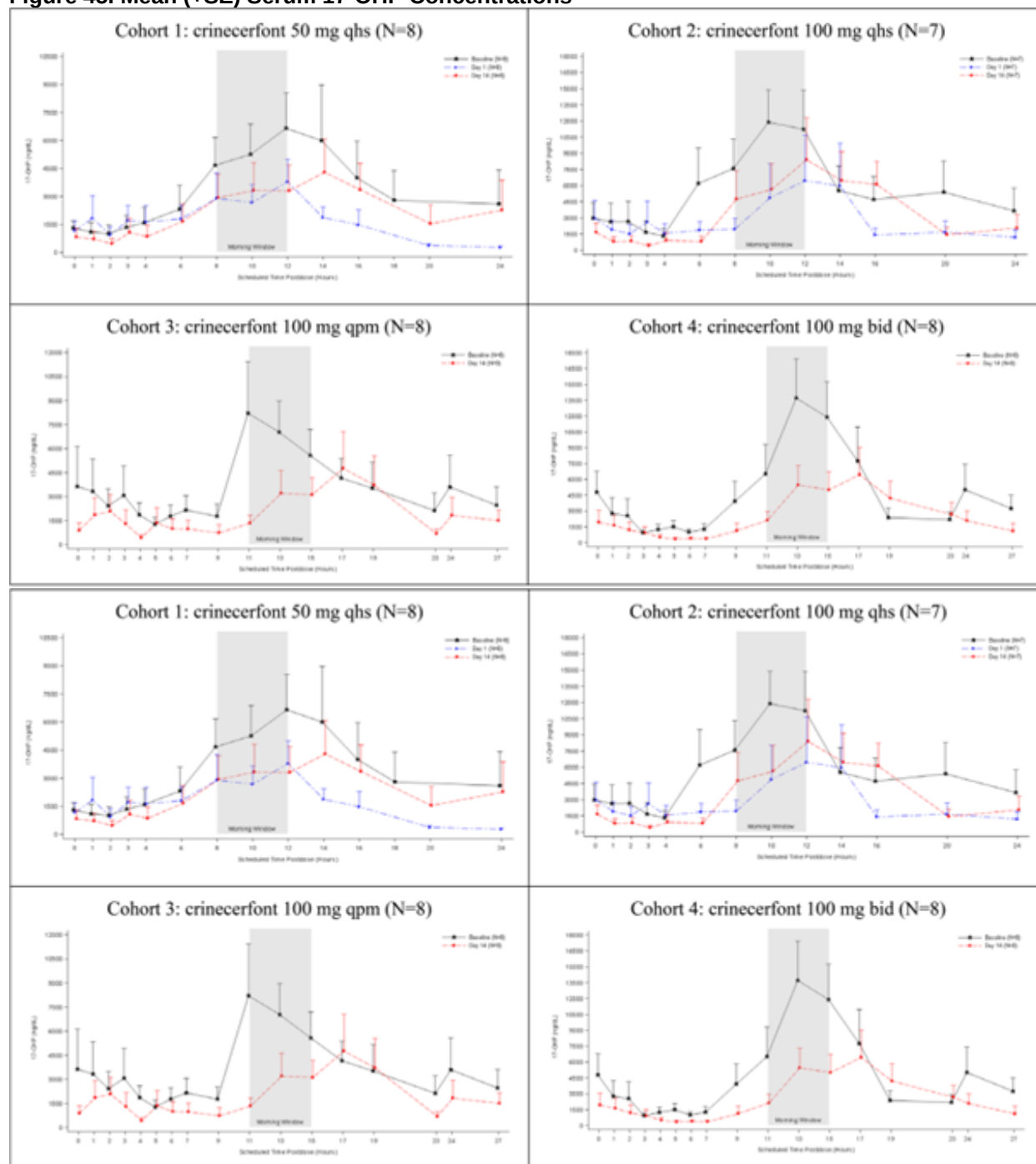
Source: Table 11, p. 60, Study NBI-74788-2001. [Link to CSR 2001](#)

Note: The PK data for T_{max}, CL/F, and fluctuation (%) were rounded to 2 significant figures and all other parameters were rounded to 3 significant figures. The last significant figure was rounded up if the digit to the right of it was ≥5 and was rounded down if the digit to the right of it was ≤4. AUC₂₄ (ng·hr/mL) for cohort 4 was calculated as AUC₀₋₁₂ (ng·hr/mL) × 2.

Abbreviations: AUC₂₄, area under the plasma concentration vs. time curve from 0 hours to 24 hours; C_{ave}, average plasma concentration; CL/F, apparent systemic clearance after oral administration; C_{max}, maximum observed plasma concentration; CSR, clinical study report; CV, coefficient of variation; max, maximum; min, minimum; PK, pharmacokinetic; qhs, nightly, at bedtime; SD, standard deviation; T_{max}, time to maximum plasma concentration

[Figure 45](#), [Figure 46](#), and [Figure 47](#) show mean concentration time profiles by cohort for 17-OHP, A4, and ACTH, respectively.

Figure 45. Mean (+SE) Serum 17-OHP Concentrations



Data Source: Figure 14.2.3

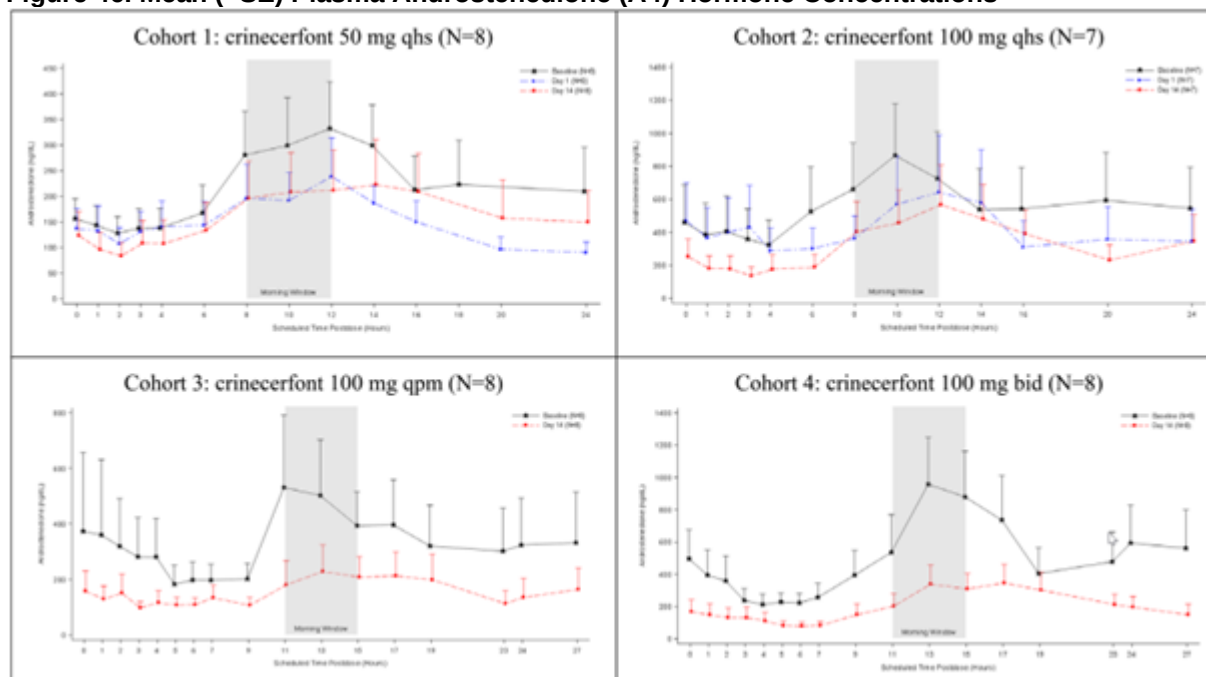
Source: Figure 3, p. 55, Study NBI-74788-2001. [Link to CSR 2001](#)

Morning window timepoints include 8, 10, and 12 hours postdose for cohorts 1 and 2 and 11, 13, and 15 hours postdose for cohorts 3 and 4.

At the PD baseline (Day -7/6) for all cohorts, morning glucocorticoid dose administration on Day -6 was delayed to approximately 1000 hours. For cohorts 1 and 2 (who had 24-hour serial sampling on Day 1/2 and Day 14/15), study drug was administered at approximately 2200 hours on Day 1 and Day 14 and morning glucocorticoid administration was delayed to approximately 1000 hours on Day 2 and to approximately 1400 hours on Day 14. For cohorts 3 and 4 (who had 24-hour serial sampling on Day 14/15), study drug was administered at approximately 1900 hours on Day 14 and morning glucocorticoid administration was delayed to approximately 1400 hours on Day 15.

Abbreviations: bid, twice daily; CSR, clinical study report; 17-OHP, 17-hydroxyprogesterone; PD, pharmacodynamic(s); qhs, nightly, at bedtime; qpm, every evening; SE, standard error

Figure 46. Mean (+SE) Plasma Androstenedione (A4) Hormone Concentrations



Data Source: Figure 14.2.5.

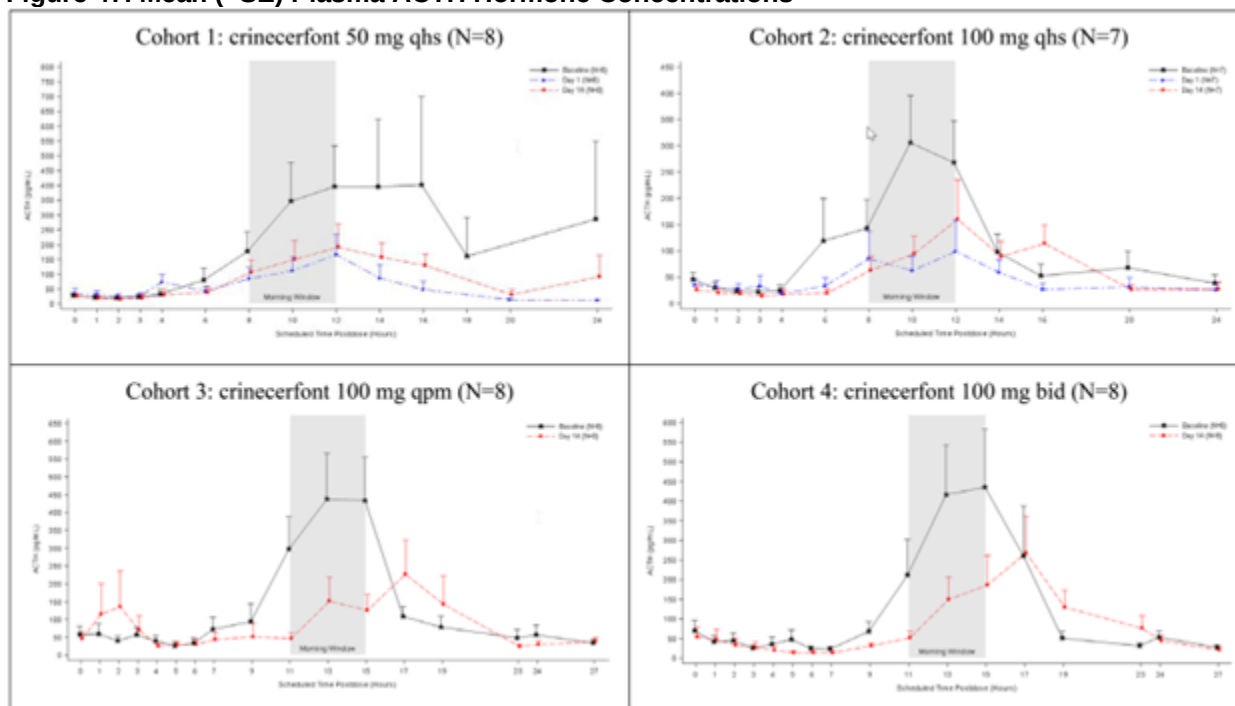
Source: Figure 4, p. 56, Study NBI-74788-2001. [Link to CSR 2001](#)

Morning window timepoints include 8, 10, and 12 hours postdose for cohorts 1 and 2 and 11, 13, and 15 hours postdose for cohorts 3 and 4.

At the PD baseline (Day -7/-6) for all cohorts, morning glucocorticoid dose administration on Day -6 was delayed to approximately 1000 hours. For cohorts 1 and 2 (who had 24-hour serial sampling on Day 1/2 and Day 14/15), study drug was administered at approximately 2200 hours on Day 1 and Day 14 and morning glucocorticoid administration was delayed to approximately 1000 hours on Day 2 and to approximately 1400 hours on Day 14. For cohorts 3 and 4 (who had 24-hour serial sampling on Day 14/15), study drug was administered at approximately 1900 hours on Day 14 and morning glucocorticoid administration was delayed to approximately 1400 hours on Day 15.

Abbreviations: bid, twice daily; CSR, clinical study report; qhs, nightly, at bedtime; qpm, every evening; SE, standard error

Figure 47. Mean (+SE) Plasma ACTH Hormone Concentrations



Data Source: Figure 14.2.1.

Source: Figure 2, p. 54, Study NBI-74788-2001. [Link to CSR 2001](#)

Morning window timepoints include 8, 10, and 12 hours postdose for cohorts 1 and 2 and 11, 13, and 15 hours postdose for cohorts 3 and 4.

At the PD baseline (Day -7/-6) for all cohorts, morning glucocorticoid dose administration on Day -6 was delayed to approximately 1000 hours. For cohorts 1 and 2 (who had 24-hour serial sampling on Day 1/2 and Day 14/15), study drug was administered at approximately 2200 hours on Day 1 and Day 14 and morning glucocorticoid administration was delayed to approximately 1000 hours on Day 2 and to approximately 1400 hours on Day 14. For cohorts 3 and 4 (who had 24-hour serial sampling on Day 14/15), study drug was administered at approximately 1900 hours on Day 14 and morning glucocorticoid administration was delayed to approximately 1400 hours on Day 15.

Abbreviation: ACTH, adrenocorticotropic hormone; bid, twice daily; qhs, nightly, at bedtime; qpm, every evening; SE, standard error

Conclusions

- The mean crinecerfont plasma concentrations increased with increasing doses.
- The AUC₂₄ 100 mg twice daily cohort (cohort 4) was approximately 2-fold higher than the AUC₂₄ 100 mg once daily cohort (cohorts 2 and 3).
- A dose-response for A4 was observed with approximately 20% median reduction from baseline with the 50 mg once-daily cohort, approximately 40% with each of the 100 mg once-daily cohorts, and approximately 60% with the 100 mg bid cohort. It should be noted that interpretation of the study results may be confounded by different baselines of clinical endpoints (e.g., serum A4), between-subject variabilities of observed clinical endpoints during study, and relatively small sample sizes across dose groups.

20.2.18. Phase 2 Dose Justification Study for Phase 3 Study in Pediatric Subjects With CAH, Trial NBI- 74788-CAH2008

Study Design

This is a phase 2, open-label, multiple-dose, dose-escalation study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of crinecerfont in pediatric subjects (14 to 16 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency (CAH) with a serum 17-OHP level of ≥ 800 ng/dL at screening. The primary objectives of this study are to assess the safety and tolerability of crinecerfont, evaluate the effect of repeated doses of crinecerfont on endogenous levels of PD biomarkers, and evaluate the PK of crinecerfont and its metabolite NBI-756179.

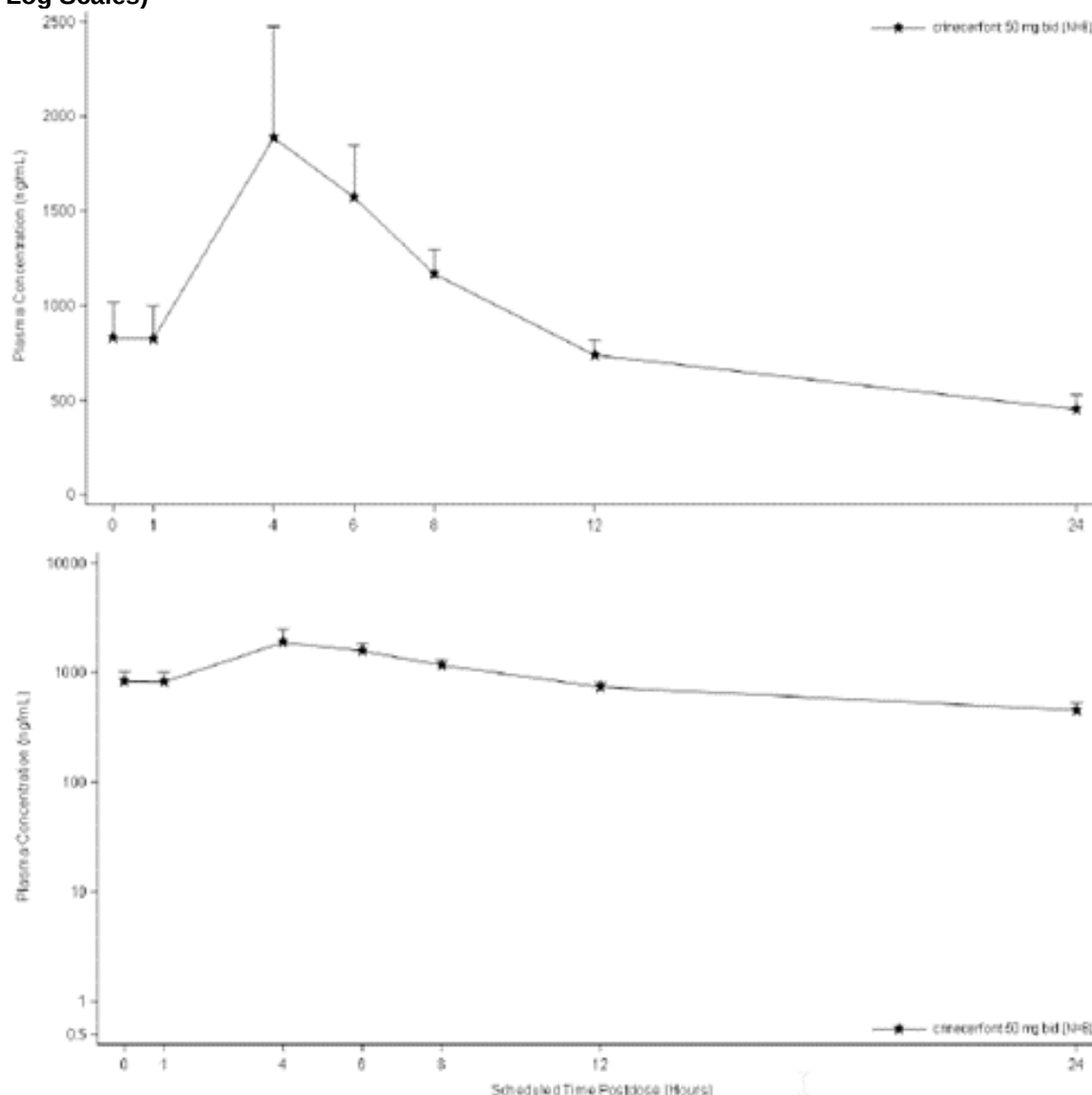
Crinecerfont was administered as 50 mg twice daily with breakfast (0700 hours) and evening meals (1900 hours). Concurrent steroidal dose was administered in the morning at approximately 1000 hours. Each dosing regimen was administered over 14 consecutive days. A total of eight subjects were enrolled and completed the study. PK samples were obtained at prespecified time points over 504 hours and plasma PK parameters were calculated for crinecerfont and metabolite NBI-756179. Primary PD samples (17-OHP) were obtained at screening and postdose at prespecified times over 15 hours. Key secondary PD samples were obtained over 24 hours to determine average 17-OHP, A4, and ACTH over 24 hours.

Results

The mean crinecerfont plasma concentration versus time profile for the four cohorts is presented in [Figure 48](#) and the summary of PK parameters for the four cohorts is presented in [Table 162](#).

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

Figure 48. Mean ($\pm$ SD) Crinecerfont Plasma Concentrations vs. Time on Days 14 to 15 (Linear and Log Scales)



Source: Figure 5, p. 37, Study NBI-74788-2008. [Link to CSR 2008](#).

Data Source: Figures 14.3.2 (linear scale) and 14.3.5 (log base 10 scale).

Crinecerfont 50 mg was administered bid at approximately 0700 hours (with breakfast) and 1900 hours (with evening meal) starting on the evening of Day 1 through the evening of Day 14. Pharmacokinetic postdose timing is relative to the evening crinecerfont dose administration (1900 hours) on Day 14.

Concentrations that are below the limit of quantification (crinecerfont <5.00 ng/mL; NBI-756179 <0.500 ng/mL) are set equal to zero

Abbreviations: bid, twice daily; CSR, clinical study report; SD, standard deviation

Table 162. Summary of Crinecerfont Plasma PK Parameters on Day 14 at 50 mg bid Dose in Pediatric Subjects

PK Parameter	50 mg bid Dose in Study NBI-74788-2008	100 mg bid Dose in Study NBI-74788-2001 ^a
AUC ₂₄ (ng·hr/mL)		
Mean (SD)	29,339 (15,618)	66,900 (20,200)
CV (%)	53.2	30.2
C _{max} (ng/mL)		
Mean (SD)	2102 (1543)	5590 (2760)
CV (%)	73.4	49.3
T _{max} (hr)		
Median (min, max)	5.0 (3.9, 6.0)	4.0 (2.0, 7.0)
CL/F (L/hr)		
Mean (SD)	4.0 (1.3)	3.2 (0.92)
CV (%)	31.8	29

Source: Compiled from Table 14.3.3, p. 157-163, Study NBI-74788-2008. [Link to CSR 2008](#).

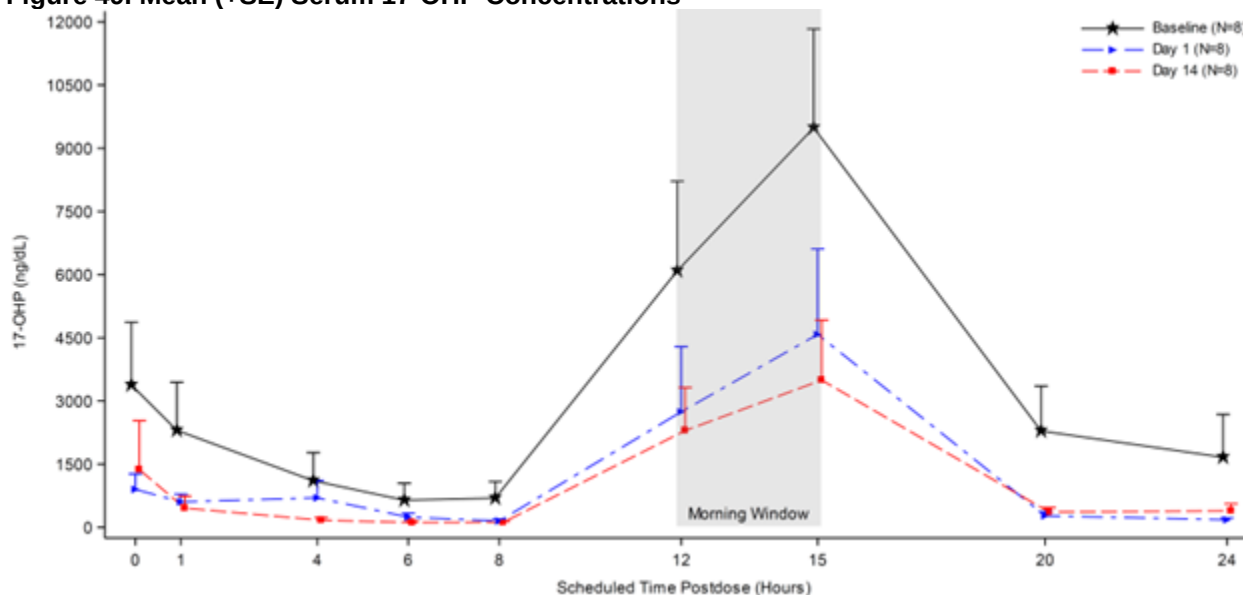
^a Data obtained from Table 11, page 60, Study NBI-74788-2001

Data from 100 mg bid dose in adults from Study NBI-74788-2001 is provided for comparative purposes.

Abbreviations: AUC₂₄, area under the concentration-time curve from 0 hours to 24 hours; bid, twice daily; CL/F, apparent systemic clearance after oral administration; C_{max}, maximum observed plasma concentration; CSR, clinical study report; CV, coefficient of variation; max, maximum; min, minimum; PK, pharmacokinetic; SD, standard deviation; T_{max}, time to maximum plasma concentration

[Figure 49](#), [Figure 50](#), and [Figure 51](#) show mean concentration time profiles for 17-OHP, A4, and ACTH, respectively.

Figure 49. Mean (+SE) Serum 17-OHP Concentrations



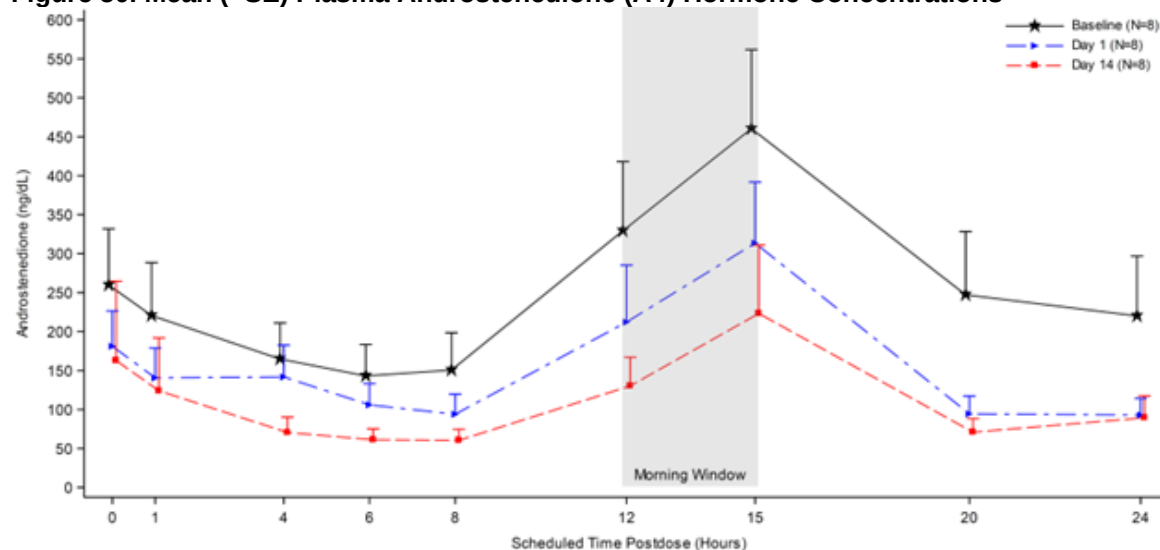
Source: Figure 14.2.2, p. 171, Study NBI-74788-2008. [Link to CSR 2008](#); Source data: ADPD

Crinecerfont 50 mg was administered bid at approximately 0700 hours (with breakfast) and 1900 hours (with evening meal) starting on the evening of Day 1 through the evening of Day 14. Pharmacodynamic postdose timing is relative to the evening crinecerfont dose administration (1900 hours).

Morning window timepoints include 12- and 15-hour postevening dose samples (0700 and 1000 hours, respectively).

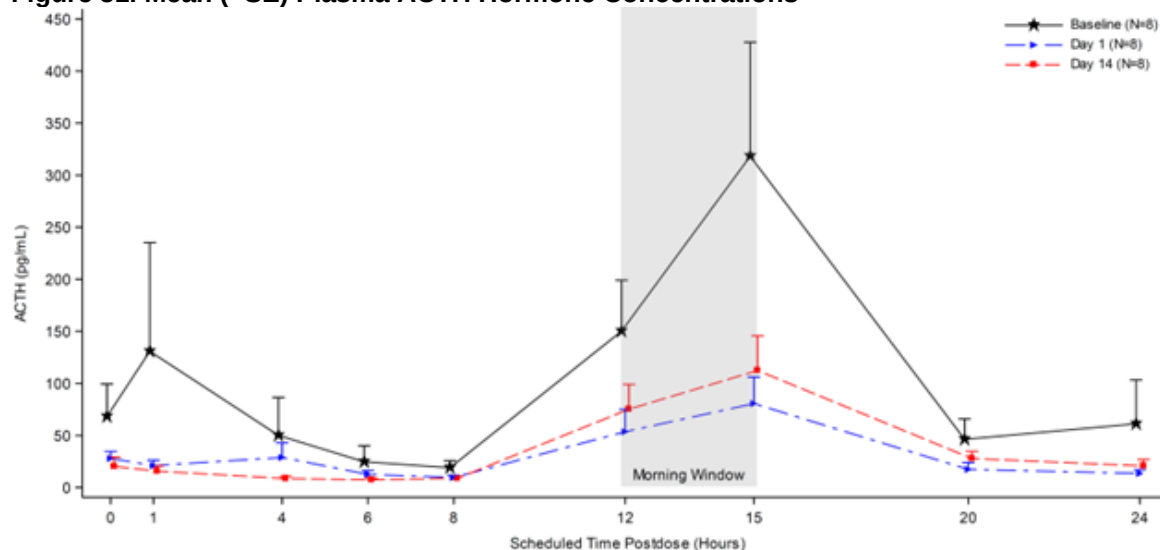
Abbreviations: bid, twice daily; CSR, clinical study report; SE, standard error; 17-OHP, 17-hydroxyprogesterone

Figure 50. Mean (+SE) Plasma Androstenedione (A4) Hormone Concentrations



Source: Figure 14.2.3, p. 172, Study NBI-74788-2008. [Link to CSR 2008](#); Source data: ADPD
Crinecerfont 50 mg was administered bid at approximately 0700 hours (with breakfast) and 1900 hours (with evening meal) starting on the evening of Day 1 through the evening of Day 14. Pharmacodynamic postdose timing is relative to the evening crinecerfont dose administration (1900 hours).
Morning window timepoints include 12- and 15-hour postevening dose samples (0700 and 1000 hours, respectively).
Abbreviations: bid, twice daily; CSR, clinical study report; SE, standard error

Figure 51. Mean (+SE) Plasma ACTH Hormone Concentrations



Source: Figure 14.2.1, p. 170, Study NBI-74788-2008. [Link to CSR 2008](#)
Abbreviations: ACTH, adrenocorticotrophic hormone; CSR, clinical study report; SE, standard error

Conclusions

- The plasma exposure (AUC) at steady state for the 50 mg twice daily dosing in subjects with CAH between 14–16 years old was approximately one-half that seen with adults with CAH at 100 mg twice daily doses.

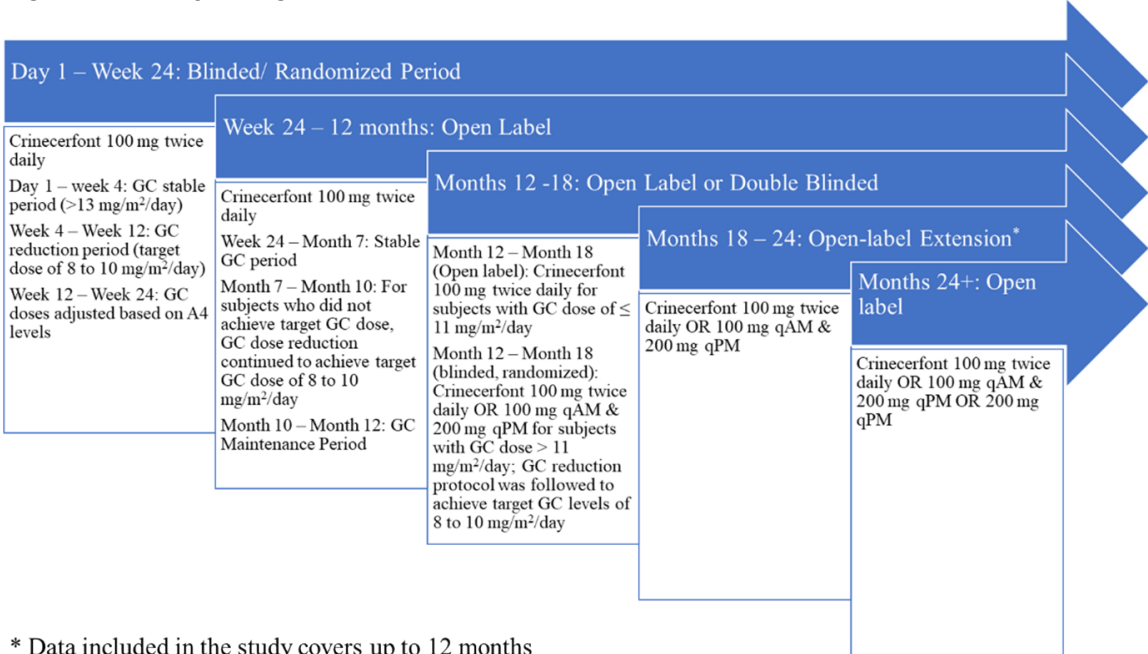
- By Day 14, ~40% reduction in the 24-hour average concentrations from baseline for PD markers 17-OHP, A4, and ACTH were observed in pediatric subjects (14 to 16 years of age) at 50 mg twice daily doses.

20.2.19. Phase 3 Study in Adults With CAH, Trial CAH3003

This is a phase 3, randomized, double-blind, placebo-controlled study to evaluate the efficacy, safety, and tolerability of crinecerfont versus placebo in 182 adult subjects with classic 21-hydroxylase deficiency (CAH). The primary objective of this study is to evaluate the efficacy of crinecerfont 100 mg twice daily in reducing daily GC dosage while maintaining adrenal androgen control. Subjects were randomized 2:1 in crinecerfont: placebo group (122:60). The study design and the doses for each period are presented in [Figure 52](#).

PK samples were obtained at prespecified time points during the study duration and plasma concentrations (ng/mL) were calculated for crinecerfont and its metabolites (NBI-756179, NBI-742939 (M4), NBI-1084059 (M9), and NBI-1084060 (M11)). The primary study endpoint was percent change from baseline (CFB) in GC daily dose at Week 24 with A4 levels controlled at $\leq 120\%$ of baseline or $\leq$ upper limit of normal (ULN) for age and sex. A key secondary endpoint was CFB in A4 levels at Week 4. Data are presented until the end of the open-label period (12 months) where 174 subjects entered the open-label period. Two subjects in the crinecerfont PK subset were not included, one due to an adverse event and another lost to follow-up, while one subject in the placebo group was not included in the analysis as they withdrew from the study.

Figure 52. Study Design and Crinecerfont Doses in Each Period, Trial NBI-74788-CAH3003



* Data included in the study covers up to 12 months

Source: Compiled from section 9, p. 21–24, Trial NBI-74788-CAH3003. [Link to CSR CAH3003](#)

Abbreviations: A4, androstenedione; CSR, clinical study report; GC, glucocorticoid; qAM, every morning; qPM, every evening

Results

The mean crinecerfont plasma concentrations by visit are presented in [Table 163](#).

Table 163. Mean Plasma Concentration (%CV) at Postbaseline Visits for Subjects Receiving Crinecerfont 100 mg bid

Visit	Plasma Concentration (ng/mL)		
	n	Mean (CV%)	Median
Double-blind period			
Week 2	116	2450.02 (57.0)	2275.00
Week 4	121	1843.73 (48.9)	1750.00
Week 6	115	2452.03 (56.6)	2270.00
Week 9	118	2504.06 (65.8)	2195.00
Week 12	120	2531.18 (57.7)	2195.00
Week 16	115	2562.44 (59.6)	2310.00
Week 20	114	2599.96 (58.7)	2370.00
Week 24	118	2029.57 (47.1)	2050.00
Open-label period			
Month 7	149	2699.33 (55.7)	2440.00
Month 8	128	2775.36 (54.4)	2535.00
Month 9	110	2700.14 (56.9)	2510.00
Month 10	100	2681.02 (61.9)	2460.00
Month 12	84	2247.06 (56.5)	2155.00

Data source: Table 14.2.22.2.1; Table 14.2.22.2.2

Source: Table 31, p. 107, Trial NBI-74788-CAH3003. [Link to CSR CAH3003](#)

Concentrations that were below the limit of quantification were set equal to zero.

At Weeks 4 and 24, the blood sample for PK measurement was collected before the morning study treatment dose.

At all other visits, the blood sample was collected at approximately the same time of the morning.

Abbreviations: bid, twice daily; CSR, clinical study report; CV, coefficient of variation; PK, pharmacokinetic

The mean (standard error of the mean [SEM]) change from study baseline for ACTH, 17-OHP, and A4 in the double-blind period and open-label period are presented in [Table 164](#).

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

Table 164. Mean (SEM) CFB at Week 4 for A4, 17-OHP, and ACTH in the Double-Blind and Open-Label Periods

Biomarkers/ Initial Treatment	Double-Blind Period				Open-Label Period			
	Week 4		Week 24		Month 7		Month 12	
	n	Mean (SEM) CFB	n	Mean (SEM) CFB	n	Mean (SEM) CFB	n	Mean (SEM) CFB
ACTH, pg/mL								
Crinecerfont	117	-75.41 (11.22)	118	-17.64 (11.34)	97	-5.42 (17.37)	59	-0.26 (19.25)
Placebo	56	-40.07 (18.24)	57	47.88 (36.33)	45	-0.29 (30.35)	28	6.49 (32.24)
17-OHP, ng/dL								
Crinecerfont	116	-2148.41 (264.11)	118	-132.86 (429.92)	94	1010.4 (708.2)	59	231.1 (785.7)
Placebo	55	-1082.55 (689.54)	57	2284.93 (933.58)	45	333.1 (943.2)	28	1154.4 (1525.6)
Androstenedione, ng/dL								
Crinecerfont	117	-187.77 (26.88)	118	-16.78 (28.55)	96	17.7 (44.2)	59	75.0 (68.4)
Placebo	56	-72.20 (40.46)	57	190.35 (56.03)	45	-39.6 (45.6)	28	78.9 (71.5)

Data Source: Table 14.2.2.1.10; Table 14.2.2.2.4; Table 14.2.13.1.9; Table 14.2.7.1.5; Table 14.2.13.2.10; Table 14.2.7.2.4

Source: Table 19, page 91. Trial NBI-74788-CAH3003. [Link to CSR CAH3003](#)

Samples were collected post-GC dose.

Baseline was defined as the last pre- or post-GC value before study treatment dosing on Day 1.

^a Results are shown for the crinecerfont group and placebo group in the double-blind period and for the crinecerfont/crinecerfont group and placebo/crinecerfont group, respectively, in the open-label period.

Abbreviations: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotrophic hormone; CFB, change from baseline; CSR, clinical study report; GC, glucocorticoid; SEM, standard error of the mean

The analysis of covariance (ANCOVA) analysis of least-squares (LS) mean (SEM) percentage of CFB for serum A4 at Week 4 for the placebo and crinecerfont groups were 21.2 (11.4) and -45.2 (7.7), respectively. The % LS mean difference (95% CI) between the crinecerfont and placebo group was -66.3% (-91.6, -41.1) with a p-value of <0.0001.³¹ The median percent change from baseline (range) after 4 weeks of dosing at 100 mg twice daily, during the GC stable phase, for ACTH was -65.8% (-98.6% to 7442.9%).

Conclusions

- By Week 2, the plasma crinecerfont 100 mg twice daily dose achieved steady state and mean plasma concentrations for crinecerfont, and its metabolites (data not shown) remained similar for the 12 months of data reported.
- The trough plasma concentration (C_{trough}) mean (% coefficient of variation [CV]) concentrations for crinecerfont at Weeks 4 and 24 were 1843.73 (48.9) and 2029.57 (47.1) ng/mL.
- At Week 4, ~66% reduction in the 24-hour average concentrations from baseline for PD marker A4 at 100 mg twice daily doses was observed.

We defer to clinical and statistical reviewers for the assessment of primary and secondary efficacy endpoints.

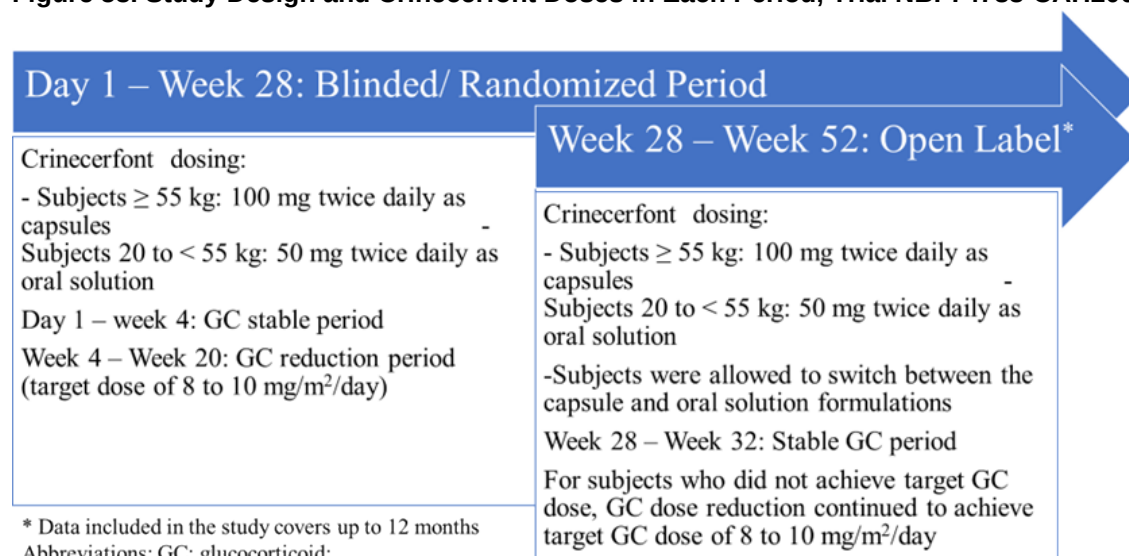
20.2.20. Phase 3 Study in Pediatric Subjects With CAH, Trial NBI-74788-CAH2006

This is a phase 3, randomized, double-blind, placebo-controlled study evaluating the efficacy, safety, and tolerability of crinecerfont versus placebo in 103 pediatric subjects with classic CAH due to 21-hydroxylase deficiency. The primary objective of this study is to evaluate the efficacy of crinecerfont in reducing adrenal steroid levels during a glucocorticoid-stable period, and key secondary objective is to evaluate the efficacy of crinecerfont in reducing daily GC dosage while maintaining adrenal androgen control. Subjects were randomized 2:1 in crinecerfont: placebo group (69:34). The study design and the doses for each period are presented in [Figure 53](#).

PK samples were obtained at prespecified time points during the study duration and plasma concentrations (ng/mL) were calculated for crinecerfont and its metabolites (NBI-756179, NBI-742939 (M4), NBI-1084059 (M9), and NBI-1084060 (M11)). The primary study endpoint was CFB in serum A4 at Week 4. The key secondary endpoint was Percent CFB in GC daily dose at Week 28, while Week 28 serum androstenedione was $\leq 120\%$ of the baseline value or $\leq \text{ULN}$, according to sex and either age (for Tanner stage 1) or pubertal stage (for Tanner stages 2 to 5). Data are presented until the end of the open-label period (12 months) where 97 subjects (66 crinecerfont: 31 placebo) entered the open-label period and all completed the study.

³¹ Source: Table 14.2.1.1.5 in supplementary analysis, page 76, Trial CAH3003

Figure 53. Study Design and Crinecerfont Doses in Each Period, Trial NBI-74788-CAH2006



Results

The mean crinecerfont plasma concentrations by visit and dose band are presented in [Table 165](#).

Table 165. Mean Plasma Concentration (%CV) at Postbaseline by Visit for Subjects Receiving Crinecerfont Twice Daily

Visit	Plasma Concentration (ng/mL)					
	Crinecerfont 50 mg bid			Crinecerfont 100 mg bid		
	n	Mean (CV [%])	Median	n	Mean (CV [%])	Median
Double-Blind Period						
Week 4 predose	34	1093.81 (57.1)	1095	32	1571.84 (60.3)	1590
Week 4 2 hours postdose	29	1679.36 (76.7)	1410	30	2368.40 (54.4)	2135
Week 4 3 hours postdose	28	1764.36 (62.9)	1730	30	2957.70 (56.4)	2970
Week 4 4 hours postdose	30	1995.54 (62.8)	1745	31	3394.52 (48.0)	2980
Week 4 6 hours postdose	29	2036.04 (54.1)	1820	31	3370.32 (47.5)	2990
Week 16 predose	32	1340.99 (48.1)	1310	27	2083.70 (32.4)	2160
Week 28 predose	34	1527.35 (40.9)	1580	29	2072.56 (38.2)	2010
Open-Label Period						
Week 40 predose	23	1289.90 (55.8)	1370	32	2085.06 (39.5)	2035
Week 52 predose	21	1393.69 (60.6)	1390	21	2050.81 (41.2)	1840

Data Source: Table 14.2.19.1.1; Table 14.2.19.2.1

Source: Table 25, p. 104, Trial NBI-74788-CAH2006. [Link to CSR 2006](#)

Note, values are based on the number of subjects with observed data for each visit at the time of data cutoff.

Subjects weighing 20 to < 55 kg received crinecerfont 50 mg bid and subjects weighing ≥ 55 kg received crinecerfont 100 mg bid.

Abbreviations: bid, twice daily; CSR, clinical study report; CV [%], percent coefficient of variation; PK, pharmacokinetic

The ANCOVA analysis of LS mean (SEM) percentage of CFB for serum A4 and 17-OHP at Week 4 and ACTH at Week 28 are presented in [Table 166](#).

Table 166. ANCOVA Analysis of Percent CFB at Week 4 for A4 and 17-OHP

Biomarkers	Placebo Group	Crinecerfont Group	% LS Mean Difference	
	% CFB LS Mean (SEM)	% CFB LS Mean (SEM)	(95% CI)	p-Value
A4	32.7 (15.4)	-53.6 (10.0)	-86.3% (-123.0, -49.6)	p<0.0001
17-OHP	19.0 (10.5)	-64.7 (7.8)	-83.6% (-109.3, -57.9)	p<0.0001

Source: Compiled from Tables 14.1.1.5 (p.75), 14.2.2.1.5 (p. 81), and 18 (p.95). Trial NBI-74788-CAH2006. [Link to CSR 2006](#)
Abbreviations: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ANCOVA, analysis of covariance; CFB, change from baseline; CI, confidence interval; CSR, clinical study report; LS, least-squares; SEM, standard error of the mean

The LS mean (SEM) change from baseline for ACTH in the double-blind period between the placebo and the crinecerfont groups were -1.47 (49.41) and -111.46 (33.48) respectively. The LS mean difference (95% CI) between the crinecerfont and the placebo group was -109.99 (-227.86, 7.89) with a p-value of 0.0671.³² The median percent change from baseline after 4 weeks of dosing at 100 mg twice daily, during the GC stable phase, for ACTH was -72%.

Conclusions

- Mean plasma concentrations for crinecerfont and its metabolites (data not shown) remained similar for the 12 months of data reported within each weight dosing band.
- Mean predose plasma concentrations of crinecerfont were similar across postbaseline assessments in the double-blind period, with mean (CV [%]) values that ranged from 1094 ng/mL (57.1%) to 1527 ng/mL (40.9%) for subjects receiving crinecerfont 50 mg twice daily (bid) and 1572 ng/mL (60.3%) to 2073 ng/mL (38.2%) for subjects receiving crinecerfont 100 mg bid.
- At Week 4, ~80% reduction in the 24-hour average concentrations from baseline for PD marker A4 and 17-OHP at 50 mg twice daily doses was observed.

20.3. Bioanalytical Method Validation and Performance

We reviewed the bioanalytical method validation reports and performance for the quantification of crinecerfont (NBI-74788I, SAR125543) and its metabolites (NBI-756179 (M6), NBI-742939 (M4), NBI-1084059 (M9), NBI-1084060 (M11)). Three LC-MS/MS methods were developed and validated for the quantitative determination of crinecerfont and its metabolite concentrations in human serum in the completed clinical studies. Detailed methods and validation parameters are described below ([Table 167](#), [Table 168](#), and [Table 169](#)). The linearity of standard curve, selectivity/specificity, assay accuracy and precision, extraction efficiency and dilution fulfilled the standard acceptance criteria. The established frozen storage stability and run storage stability covered the corresponding study period and sample analysis period. We determined that these method validation and sample analysis are acceptable.

³² Source: Table 18, page 95, Trial CAH2006

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Table 167. Bioanalytical Method Validation for the Determination of Crinecerfont and Metabolite M4 in Human Plasma

Analyte	Crinecerfont	M4
Bioanalytical method validation report name, study number supported, and hyperlinks	Validation Report No: 11352.042617 [NBI-74788-1601] Validation Report No (full): 11352.042617 ; Validation Report No (partial): 12555.062218 Bioanalytical reports: NBI-74788-1601: 11423.051917 NBI-74788-1704: 12807.071818 NBI-74788-1712: 13880.032619 NBI-74788-1716: 14941.210819 NBI-74788-1717: 15098.270919 NBI-74788-1718: 15091.010320 NBI-74788-1734: 16884.201020.1 NBI-74788-2001: 11914.101218 NBI-74788-2008: 14707.120619	
Method description	Protein precipitation followed by LC-MS/MS	
Stability in human plasma at room temperature (h)	26	26
Process extract stability at 10°C (h)	82	82
Standard Calibration Curve		
Performance During Accuracy and Precision Runs		
	Validation Parameters	
LLOQ (ng/mL)	5.00	0.5
Validated range (ng/mL)	5.00 to 2500	0.500 to 250
Within-run precision (%)	≤4.0	≤7.3
Between-run precision (%)	≤3.6	≤5.0
Accuracy (% bias)	-10.4 to 7.4	-7.0 to 5.0
Incurred Sample Reanalysis Within Acceptance Criteria (±20%)		
NBI-74788-1601	93.4% (57/61)	93.4% (57/61)
NBI-74788-1704	89.5% (136/152)	84.9% (129/152)
NBI-74788-1712	94.6% (105/111)	99.1% (111/112)
NBI-74788-1716	86.9% (139/160)	92.5% (148/160)
NBI-74788-1717	89.1% (41/46)	79.2% (38/48)
NBI-74788-1718	70.6% (48/68)	74.3% (52/70)
NBI-74788-1734	95.1% (98/103)	Not quantified
NBI-74788-2001	82.9% (68/82)	88.0% (73/83)
NBI-74788-2008	100% (23/23)	95.7% (22/23)
Long term stability (-80°C) (days)	393	393
Freeze/thaw cycles (-80°C)	5	5
Maximum Duration Between Sample Draw and Analysis (Days)		
NBI-74788-1601	71	
NBI-74788-1704	82	
NBI-74788-1712	102	
NBI-74788-1716	104	
NBI-74788-1717	407*	
NBI-74788-1718	68	
NBI-74788-1734	139	
NBI-74788-2001	364	
NBI-74788-2008	343	

Source: FDA reviewer's table

* NBI-74788-1717 time between the sample draw and analysis exceeds the maximum stability of 393 days

Abbreviations: LC-MS/MS, liquid chromatograph-mass spectrometry; LLOQ, lower limit of quantification

Table 168. Bioanalytical Method Validation for the Determination of Crinecerfont and Its Metabolites NBI-756179 (M4), NBI-742939 (M6), NBI-1084059 (M9), and NBI-1084060 (M11) in Human Plasma

Analyte	Crinecerfont	M4	M6	M9	M11
Bioanalytical method validation report name, study number supported, and hyperlinks	Validation Report No: 17000.061120.1 Bioanalytical reports: NBI-74788-1719: 19844.090622 NBI-74788-1724: 16678.080920 NBI-74788-1736: 18123.110621 NBI-74788-3003 [interim report]: 16065.070520.INT1 NBI-74788-2006 [interim report]: 17452.120221.INT1				
Method description	Protein precipitation followed by LC-MS/MS				
Stability in human plasma at room temperature (h)	26	26	29	29	29
Process extract stability at 10°C (h)	94	87	78	78	78
Standard Calibration Curve Performance During Accuracy and Precision Runs					
	Validation Parameters				
LLOQ (ng/mL)	5.00	0.500	0.500	0.500	0.500
Validated range (ng/mL)	5.00 to 5000	0.500 to 500	0.500 to 500	0.500 to 500	0.500 to 500
Between-run precision (%)	≤6.2	≤4.5	≤6.8	≤4.6	≤5.3
Accuracy (% bias)	-5.5 to 3.0	-4.3 to 3.0	-2.3 to 1.5	-2.3 to 3.0	-1.3 to 1.2
Incurred Sample Reanalysis Within Acceptance Criteria (±20%)					
NBI-74788-1719	98.5% (128/130)	97.7% (127/130)	91.5% (119/130)	100% (130/130)	92.3% (120/130)
NBI-74788-1724	90.0% (108/120)	92.5% (111/120)	96.7% (116/120)	96.6% (115/119)	72.3% (86/119)
NBI-74788-1736	96.5% (164/170)	Not quantified	Not quantified	Not quantified	Not quantified
NBI-74788-3003	97.3% (179/184)	96.7% (178/184)	96.7% (178/184)	97.8% (179/183)	98.9% (176/178)
NBI-74788-2006	94.6% (35/37)	92.1% (35/38)	94.6% (35/37)	94.7% (36/38)	94.7% (36/38)
Long term stability (-80°C)	792	788	788	788	788
Freeze/thaw cycles (-80°C)	6	6	6	6	6
Maximum Duration Between Sample Draw and Analysis (Days)					
NBI-74788-1719	119				
NBI-74788-1724	70				
NBI-74788-1736	63				
NBI-74788-3003	442				
NBI-74788-2006	233				

Source: FDA reviewer's table

Abbreviations: LLOQ, lower limit of quantification; LC-MS/MS, liquid chromatograph-mass spectrometry

Table 169. Bioanalytical Method Validation for the Determination of Crinecerfont in Human Plasma. (Studies Conducted by Sanofi SA)

Analyte	Crinecerfont
Bioanalytical method validation report name, study number supported, and hyperlinks	Validation Report No: DOH0650 [for BEX5094] Validation Report No: DOH0286 BEX5094 (in CSR): RPSMPK-BEX5094-BA1-EN-E01 INT5449 (in CSR): RPSMPK-INT5449-BA1-EN-E01 INT11387 (in CSR): Phase Report Bioanalysis - INT11387 - BA1 - SSR125543 INT6752 (in CSR): Phase Report Bioanalysis - Study Code - BA1 - SSR125543 GAR6751 (in CSR): SSR125543-GAR6751-BA1-ENE01 TDU10479 (in CSR): RPSMPK-TDU10479-BA1-EN-E01
Method description	Protein precipitation followed by LC-MS/MS
Stability in human plasma at room temperature (h)	72
Process extract stability at 10°C (h)	168
Standard Calibration Curve Performance During Accuracy and Precision Runs	
Validation Parameters	
LLOQ (ng/mL)	5.00
Validated range (ng/mL)	5.00 to 2500
Within-run precision (%)	≤8.89
Between-run precision (%)	≤3.40
Accuracy (% bias)	1.54 to 6.87
Incurred Sample Reanalysis Within Acceptance Criteria (±20%)	
BEX5094	98.0% (49/50)
INT5449	98.0% (49/50)
INT11387	86.7% (39/45)
INT6752	100% (49/49)
GAR6751	Not available
TDU10479	84% (42/50)
Long-term stability (-20°C) (months)	40
Freeze/thaw cycles (-80°C)	4
Maximum Duration Between Sample Draw and Analysis (Days)	
BEX5094	Within 24 months for incurred samples and 7 months for spiked samples
INT5449	Within 24 months for incurred samples and 12 months for spiked samples
INT11387	Within 24 months for incurred samples and 12 months for spiked samples
INT6752	Within 24 months for incurred samples and 12 months for spiked samples
GAR6751	Within 3 months
TDU10479	Within 5 months

Source: FDA reviewer's table

Abbreviations: CSR, clinical study report; LLOQ, lower limit of quantification; LC-MS/MS, liquid chromatograph-mass spectrometry

PD Markers Validation Reports for ACTH, 17-OHP, and A4

We reviewed the biomarker analytical method summary for ACTH ([Table 170](#)), 17-OHP ([Table 171](#)), and A4 ([Table 171](#)) and determined them to be acceptable.

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Table 170. ACTH Biomarker Analytical Method Summary

Analyte	Adrenocorticotrophic Hormone (ACTH)
Matrix	EDTA plasma
Analytical method	Electrochemiluminescence immunoassay (ECLIA)
Manufacturer	(b) (4)
Controls	(b) (4)
Precision	Within-run: 0.5 to 2.6% CV; 0.26 SD for low QC Between-run: 2.8 to 4.1% CV; 0.13 SD for low QC
Analytical measuring range (AMR)	2.7 to 2000.0 pg/mL
LLOQ	2.7 pg/mL
Accuracy	-7.4 to -0.1% bias

Source: Module 5.3.1.4 ACTH Summary Validation Report

Abbreviations: CV, coefficient of variation; LLOQ, lower limit of quantification; (b) (4) QC, quality control; SD, standard deviation

Table 171. 17-Hydroxyprogesterone (17-OHP) and Androstenedione (A4) Bioanalytical Method Summary

Specimen Type	Human Serum (Red Top) and Plasma (EDTA and Heparin)			
Intra-assay precision	Summary Androstenedione	Level 1	Level 2	Level 3
	Grand mean, ng/dL	11.23	172.48	445.40
	CV%	8.08%	3.69%	4.91%
	Summary 17-Hydroxyprogesterone	Level 1	Level 2	Level 3
	Grand mean, ng/dL	51.90	226.61	3573.71
	CV%	7.65%	4.88%	4.30%
Interassay precision	Summary Androstenedione	Level 1	Level 2	Level 3
	Grand mean, ng/dL	16.15	200.64	491.45
	CV%	7.32%	3.47%	3.68%
	Summary 17-Hydroxyprogesterone	Level 1	Level 2	Level 3
	Grand mean, ng/dL	51.14	208.17	3574.13
	CV%	7.11%	5.65%	6.10%
Method comparison	The split-sample comparison studies linear regressions: RIA vs. LC-MS/MS ANDRO: $0.8289x + 0.5089$; $r^2=0.9280$ RIA vs. LC-MS/MS 17-OHP: $0.8007x + 12.465$; $r^2=0.8973$ Deuterated IS vs. $^{13}\text{C}_3$ IS ANDR: $1.0638x + 0.76$; $r=0.9926$ Deuterated IS vs. $^{13}\text{C}_3$ IS 17-OHP: $1.0373 - 2.80$; $r=0.9962$			
Measurement uncertainty	Androstenedione Low-High CI, ng/dL	Level 1	Level 2	Level 3
	MU lower 95 th percentile CI	9.19	149.29	396.61
	MU higher 95 th percentile CI	13.27	195.66	494.19
	17-Hydroxyprogesterone Low-High CI, ng/dL	Level 1	Level 2	Level 3
	MU lower 95 th percentile CI	42.39	202.01	3279.71
	MU higher 95 th percentile CI	61.41	251.22	3867.70
Recovery study	ANDRO and 17-OHP recovery bias was acceptable.			

Specimen Type	Human Serum (Red Top) and Plasma (EDTA and Heparin)	
Analytical sensitivity (<i>limit of detection</i>)		ANDRO
		17-OHP
	Limit of blank (LOB)	2.166 ng/dL
	Limit of detection (LOD)	3.924 ng/dL
Analytical sensitivity (<i>limit of quantitation</i>)		ANDRO
		17-OHP
	Limit of quantitation (LOQ)	5 ng/dL
Analytical specificity (<i>cross reactivity</i>)	No cross reactivity was detected.	
Analytical specificity (<i>interference</i>)	No interference was detected.	
Linearity	The assay linearity was verified for the AMR	
Analytical measurement range (AMR)	ANDRO: AMR =5–5,000 ng/dL	
	17-OHP: AMR =8–5,000 ng/dL	
Reportable range (RR)	ANDRO: RR =5–25,000 ng/dL	
	17-OHP: RR =8–50,000 ng/dL	
Carryover	No carryover was observed for this assay.	

Source: Module 5.3.1.4 17-OHP and A4 Summary Validation Report

Abbreviations: ANDRO, androstenedione; CI, confidence interval; CV, coefficient of variation; IS, internal standard; LC-MS/MS, liquid chromatograph-mass spectrometry; MU, measurement uncertainty; RIA, radioimmunoassay

20.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Not applicable.

20.5. Pharmacometrics Assessment

20.5.1. Review Summary

Crinecerfont is a selective CRF1 antagonist indicated (b) (4)

To support the proposed marketed dose, (i.e., clinical doses evaluated in phase 3 studies), the Applicant conducted popPK modeling and exposure-response (E-R) efficacy analyses. Additionally, E-R safety analyses were also explored for select safety endpoints.

In general, the Applicant's popPK analysis is considered acceptable for characterization of crinecerfont pharmacokinetics, evaluation of impact of clinically relevant covariates, and generation of exposure metrics for E-R analyses for safety and efficacy in the target adult and pediatric CAH populations. We verified the Applicant's analyses, and no significant discordance was identified. More specifically, the developed model was used to support the current submission as outlined in [Table 172](#).

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Table 172. Specific Comments on Applicant's Final PopPK Model

Utility of the Final Model		Reviewer's Comments
Support Applicant's proposed labeling statements about intrinsic and extrinsic factors	Intrinsic factor <u>Section 8.7</u> (b) (4) CRENESSITY is not recommended in patients with severe renal impairment or end-stage renal disease. <u>Section 12</u> (b) (4)	The statement is acceptable. Based on assessment of covariate impact (Figure 58), no clinically significant difference in crinecerfont PK is observed with renal impairment (mild or moderate) or age. The covariate effect of sex and race were not retained in the final population PK model and are not expected to have clinically significant impact on crinecerfont PK.
	Extrinsic factor	N/A
Derive exposure metrics for exposure-response analyses	Model-predicted steady-state C_{min} , C_{max} , C_{avg} , and 24-hour AUC	The Applicant's final model is generally acceptable for generating exposure metrics to describe crinecerfont PK and perform E-R analyses for safety and efficacy.
Predict exposures at alternative dosing regimen	Steady-state C_{max} and 24-hour AUC for 37.5 mg twice daily and 50 mg twice daily	Using the final popPK model, simulated alternative regimens of 37.5 mg twice daily and 50 mg twice daily (oral solutions) had improved AUC and C_{max} relative to those of the reference population of 20 to <55 kg; however, relatively higher proportions of the simulated subjects (10 to <20 kg) were also projected to have exposures above the 95 th percentile of the reference exposures. Therefore, 25 mg bid (for the 10 to <20 kg subgroup) is expected to produce similar exposures to those of the 50 mg bid (for the 20 to <55 kg subgroup).

Source: Compiled by reviewer

Abbreviations: AUC, area under the concentration-time curve; bid, twice daily; C_{avg} , average observed plasma concentration; C_{max} , maximum observed plasma concentration; C_{min} , minimum observed plasma concentration; E-R, exposure-response; PK, pharmacokinetic; popPK, population PK; N/A, not applicable

20.5.2. Introduction

The primary objectives of the Applicant's analysis were to:

- Develop a popPK model to characterize crinecerfont pharmacokinetics in healthy subjects and adult and pediatric subjects with CAH
- Evaluate the covariate effects on crinecerfont pharmacokinetics
- Generate individual crinecerfont PK exposure metrics for E-R analyses for safety and efficacy

20.5.3. Model Development

Data

The popPK analysis was based on PK data from four phase 1 studies in healthy subjects, two phase 2 studies, and two phase 3 studies in subjects with CAH. The study design, study population, dose levels, drug formulation, and type of PK samples are summarized in [Table 173](#). For clinical studies that were excluded and the associated rationale, details can be found in Section 3.1 in the Applicant's popPK report.

The final nonlinear mixed-effects modeling (NONMEM) data file for analysis contained 6647 PK observations from 342 unique subjects ([Table 174](#)). Note that nine subjects were included in both phase 2 and phase 3 studies, contributing to 351 subjects in the summary tables. [Table 175](#) provides summary statistics of the baseline demographic covariates in the analysis dataset.

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Table 173. Summary of Clinical Studies Included in the PopPK Analysis

Study	Title	Number of Subjects	Dose Levels	PK Sampling	Single or Multiple Dose	Formulation
TDR10671 (phase 1)	Randomized, double-blind, placebo-controlled study of the tolerability and pharmacokinetics of 14-day repeated ascending oral doses of SSR125543 in healthy young male subjects.	48	20 mg, 50 mg, 100 mg, 200 mg qd with MFB in 14-day cycles	Serial	Multiple dose	(b) (4) in hard gelatin capsule (phase 2 (b) (4) capsule)
TDU10479 (phase 1)	A single oral ascending dose, safety, tolerability, and pharmacokinetic study of SSR125543 in healthy young male subjects.	64	20 mg and 50 mg fasted 20 mg, 50 mg, 100 mg, 200 mg, 400 mg, 800 mg with MFB.	Serial	Single dose	(b) (4) in hard gelatin capsule (phase 2 (b) (4) capsule)
NBI-74788-1724 (phase 1)	A phase 1, randomized, double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of crinecerfont in healthy subjects	30	250 mg with standard meal (100 mg qAM and 150 mg qPM) 300 mg with standard meal (100 mg qAM and 200 mg qPM)	Serial and sparse	Multiple dose	(b) (4) in hard gelatin capsule (phase 3 capsule)
NBI-74788-1716 (phase 1)	A phase 1, open-label study to evaluate the pharmacokinetics, relative bioavailability, effect of food, safety, and tolerability of different NBI-74788 prototype formulations in healthy adult subjects	36	50 mg or 100 mg with Ensure Plus	Serial	Single dose	(b) (4) in hard gelatin capsule (phase 2 (b) (4) capsule), oral solution Alternate formulations evaluated in the study were not included in analyses

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Study	Title	Number of Subjects	Dose Levels	PK Sampling	Single or Multiple Dose	Formulation
CAH2001 (phase 2)	A phase 2, open-label, multiple-dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of crinecerfont in adult subjects with congenital adrenal hyperplasia	18	Cohort 1: 50 mg qd with Ensure Plus Cohort 2: 100 mg qd with Ensure Plus Cohort 3: 100 mg qd with standard meal Cohort 4: 100 mg bid with standard meal	Serial	Multiple dose	(b) (4) in hard gelatin capsule (phase 2 (b) (4) capsule)
CAH2008 (phase 2)	A phase 2, open-label, multiple-dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of NBI-74788 in pediatric subjects with congenital adrenal hyperplasia	8	50 mg bid with standard meal (calorie unspecified)	Serial	Multiple dose	(b) (4) in hard gelatin capsule (phase 2 (b) (4) capsule)
CAH3003 (phase 3)	A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of crinecerfont (NBI-74788) in adult subjects with classic congenital adrenal hyperplasia, followed by open-label treatment	182	100 mg bid or placebo with standard meal (calorie unspecified)	Sparse	Multiple dose	(b) (4) in hard gelatin capsule (phase 3 capsule)

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Study	Title	Number of Subjects	Dose Levels	PK Sampling	Single or Multiple Dose	Formulation
CAH2006 (phase 3)	A randomized, double-blind, placebo-controlled study to evaluate the safety and efficacy of crinecerfont (NBI-74788) in pediatric subjects with classic congenital adrenal hyperplasia, followed by open-label treatment	103	25 mg bid via oral solution for subjects 10 to <20 kg 50 mg bid via oral solution for subjects 20 to <55 kg 100 mg bid via oral capsules for subjects ≥55 kg or matching placebos. Taken with standard meal (calorie unspecified)	Sparse	Multiple dose	(b) (4) in hard gelatin capsule (phase 3 capsule) and oral solution

Source: Applicant's popPK report, Table 3.1, pages 23-26

SSR125543 = NBI-74788 = crinecerfont

Abbreviations: bid, twice daily; CAH, congenital adrenal hyperplasia; MFB, moderate fat breakfast; PK pharmacokinetic; qAM, every morning; qd, once daily; qPM, every evening;

(b) (4); popPK, population PK

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The pooled PK data for crinecerfont consists of PK observations from multiple dose levels and from different formulations across adult and pediatric populations of both healthy and CAH status. In addition, both serial and sparse PK were obtained. Additional covariates were also available for assessment of covariate impact. Overall, the pooled data are adequate in popPK modeling and describing crinecerfont disposition in adult and pediatric subjects with CAH.

Table 174. Summary of PK Observations by Study

Study	Number				Percent	
	SUBJ	MISS	OBS	BLQ	OBS	BLQ
NBI-74788-1716	35	0	662	141	9.2	2.0
NBI-74788-1724	20	0	1130	14	15.7	0.2
NBI-74788-CAH2001	18	0	782	10	10.8	0.1
NBI-74788-CAH2008	8	0	129	3	1.8	0.0
TDU10479	48	0	1140	184	15.8	2.6
TDR10671	32	0	1514	117	21.0	1.6
NBI-74788-CAH3003	121	0	862	96	12.0	1.3
NBI-74788-CAH2006	69	0	428	1	5.9	0.0
All data	351	0	6647	566	92.2	7.8

Source: Applicant's popPK report, Table 5.1, page 35

Abbreviations: BLQ, below limit of quantitation; MISS, missing; OBS, observations; PK, pharmacokinetic; popPK, population PK; SUBJ, subjects

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Table 175. Summary of Baseline Characteristics for PopPK Population

Characteristic	Adult (N=274)	Ped ≥55 kg (N=36)	Ped 20 to <55 kg (N=41)	Overall (N=351)
Age (years)				
Mean (SD)	31.9 (9.95)	14.0 (2.06)	10.1 (3.27)	27.5 (12.2)
Median [min, max]	30.0 [18.0, 54.0]	14.5 [8.00, 17.0]	10.0 [5.00, 17.0]	26.0 [5.00, 54.0]
Weight (kg)				
Mean (SD)	78.1 (14.6)	70.6 (12.5)	42.4 (9.56)	73.1 (18.0)
Median [min, max]	77.4 [44.8, 136]	66.5 [55.3, 115]	44.4 [20.5, 58.7]	73.6 [20.5, 136]
Missing	8 (2.9%)	0 (0%)	0 (0%)	8 (2.3%)
Sex				
Female	106 (38.7%)	15 (41.7%)	24 (58.5%)	145 (41.3%)
Male	168 (61.3%)	21 (58.3%)	17 (41.5%)	206 (58.7%)
Race				
American Indian or Alaska Native	1 (0.4%)	1 (2.8%)	0 (0%)	2 (0.6%)
Asian	9 (3.3%)	5 (13.9%)	3 (7.3%)	17 (4.8%)
Black or African American	31 (11.3%)	2 (5.6%)	1 (2.4%)	34 (9.7%)
Multiple	1 (0.4%)	0 (0%)	3 (7.3%)	4 (1.1%)
Other	5 (1.8%)	1 (2.8%)	2 (4.9%)	8 (2.3%)
White	223 (81.4%)	23 (63.9%)	26 (63.4%)	272 (77.5%)
Missing	4 (1.5%)	4 (11.1%)	6 (14.6%)	14 (4.0%)
Disease status				
Healthy	135 (49.3%)	0 (0%)	0 (0%)	135 (38.5%)
CAH	139 (50.7%)	36 (100%)	41 (100%)	216 (61.5%)
Formulation				
Oral solution	6 (2.2%)	0 (0%)	37 (90.2%)	43 (12.3%)
Phase 2 (b) (4) cap	18 (6.6%)	6 (16.7%)	2 (4.9%)	26 (7.4%)
Phase 2 (b) (4) cap	109 (39.8%)	0 (0%)	0 (0%)	109 (31.1%)
Phase 3 cap	141 (51.5%)	30 (83.3%)	2 (4.9%)	173 (49.3%)
Food status				
Ensure	50 (18.2%)	0 (0%)	0 (0%)	50 (14.2%)
Fasted	12 (4.4%)	0 (0%)	0 (0%)	12 (3.4%)
Fed calorie unspecified (standard meal)	121 (44.2%)	36 (100%)	41 (100%)	198 (56.4%)
Moderate fat breakfast	71 (25.9%)	0 (0%)	0 (0%)	71 (20.2%)
Standard meal	20 (7.3%)	0 (0%)	0 (0%)	20 (5.7%)
Baseline eGFR (mL/min/1.73 m ²)				
Mean (SD)	112 (16.7)	108 (23.7)	118 (26.3)	113 (19.0)
Median [min, max]	112 [43.8, 158]	104 [73.3, 160]	113 [61.3, 186]	112 [43.8, 186]
Missing	8 (2.9%)	0 (0%)	0 (0%)	8 (2.3%)

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Characteristic	Adult (N=274)	Ped ≥55 kg (N=36)	Ped 20 to <55 kg (N=41)	Overall (N=351)
Baseline total bilirubin (mg/dL)				
Mean (SD)	0.614 (0.319)	0.517 (0.247)	0.500 (0.249)	0.590 (0.307)
Median [min, max]	0.532 [0.0990, 1.86]	0.485 [0.200, 1.28]	0.439 [0.187, 1.39]	0.520 [0.0990, 1.86]
Missing	8 (2.9%)	0 (0%)	0 (0%)	8 (2.3%)
Baseline AST (U/L)				
Mean (SD)	18.9 (6.18)	15.9 (4.55)	18.3 (4.50)	18.5 (5.91)
Median [min, max]	17.0 [9.00, 38.0]	15.0 [9.00, 29.0]	18.0 [11.0, 33.0]	17.0 [9.00, 38.0]
Missing	11 (4.0%)	0 (0%)	0 (0%)	11 (3.1%)
Baseline ALT (U/L)				
Mean (SD)	20.2 (9.76)	15.0 (8.15)	13.0 (4.61)	18.8 (9.50)
Median [min, max]	18.0 [5.00, 58.0]	12.5 [5.00, 47.0]	12.0 [8.00, 27.0]	16.0 [5.00, 58.0]
Missing	9 (3.3%)	0 (0%)	0 (0%)	9 (2.6%)

Source: Reviewer's analysis based on Applicant's submitted dataset

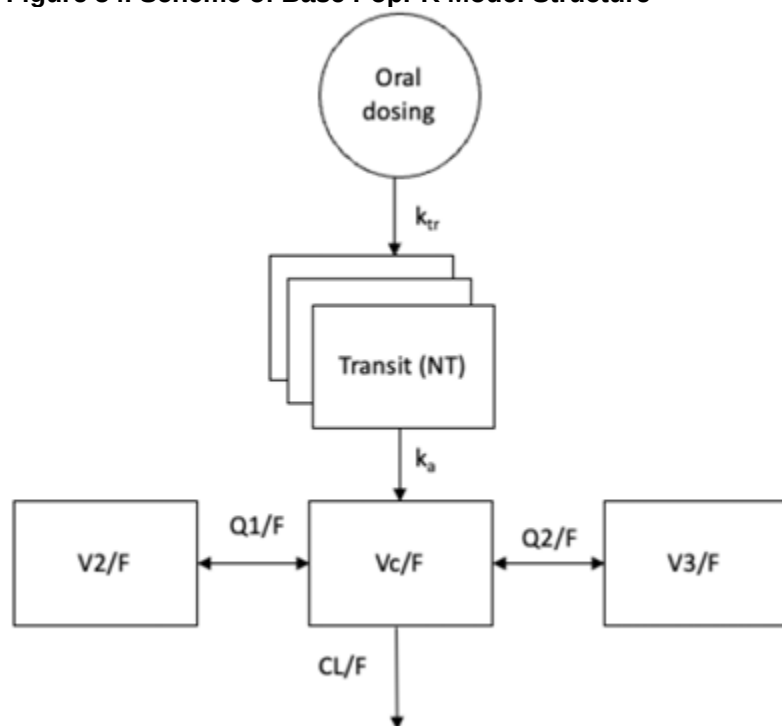
CKD-EPI 2009 equation was used for adult subjects; bedside Schwartz equation was used for pediatric subjects (≤18 years); total sample size includes 9 PK evaluable subjects who were enrolled in both phase 2 and phase 3 studies

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; popPK, population pharmacokinetic(s); SD, standard deviation

Base Model

The base model was a three-compartment popPK model with transit compartment absorption and linear clearance. Interindividual variability (or random effects) was modeled assuming a log-normal distribution for patient level random effects. Residual variability was described using a log-additive error model during model development and subsequent model runs. Model evaluation and selection of the base model were based on standard statistical criteria of goodness-of-fit, diagnostic plots, significant reductions in objective function value, accuracy of parameter estimation (i.e., 95% confidence interval excluding 0), successful model convergence, and diagnostic plots.

Figure 54. Scheme of Base PopPK Model Structure



Source: Applicant's popPK report, Figure 5.1, page 37

Abbreviations: k_{tr} , transit compartment rate constant; k_a , absorption rate constant; NT, number of transit compartments; V_c/F , apparent central volume of distribution; V_2/F and V_3/F , apparent peripheral volumes of distribution; $Q1/F$ and $Q2/F$, apparent intercompartmental clearance; CL/F , apparent drug clearance; popPK, population pharmacokinetic(s)

Covariate Analysis

Covariate-parameter relationships were investigated and identified using clinical and physiologic relevance, exploratory analysis, prior knowledge, and mechanistic plausibility. Collinearity of covariates was assessed to ensure that no collinear covariates were added to the model. An assessment of any remaining trends was conducted by graphical inspection of covariate effects (plots of maximum a posteriori Bayes estimates of individual random effects and/or normalized prediction distribution error versus covariates). Continuous covariates were evaluated using a power function, and categorical covariates were parameterized as a fractional change.

In addition to the covariates listed in [Table 176](#), any remaining trends in random effects for dexamethasone use and Tanner stage were examined in a post hoc exploratory graphical

analysis. Only a limited number of subjects in the dataset (n=17) received concomitant dexamethasone at baseline (≤ 1 mg total daily dose) with crinecerfont.

Table 176. Candidate Covariates for Model Development

PK Parameter	Covariates
Absorption parameters (K_a , MTT)	Food status (fasted versus fed), formulation (capsule versus oral solution)
F	Food status (fasted versus fed), formulation (capsule versus oral solution)
CL/F	Sex, race, age, disease status (healthy versus CAH), baseline body weight, baseline clinical laboratory parameters for hepatic function (ALT, AST, total bilirubin) and renal function (e.g., CrCL, eGFR), baseline albumin
V/F	Sex, race, age, disease status (healthy versus CAH), baseline body weight, baseline albumin
Q/F	Baseline body weight

Source: Applicant's popPK report, Table 4.1, page 31

Abbreviations: ALT, alanine transaminase; AST, aspartate aminotransferase; CAH, congenital adrenal hyperplasia; CL/F, apparent clearance; CrCL, creatinine clearance; eGFR, estimated glomerular filtration rate; F, relative oral bioavailability; K_a , absorption rate constant; MTT, mean transit time; PK, pharmacokinetic; popPK, population PK; Q/F, apparent intercompartmental clearance; V/F, apparent volume of distribution

20.5.4. Final Model

The final popPK model included fixed effects of body weight on clearance and volume of distribution-related terms. For pediatric subjects under 18 years of age, time-varying body weight was used. For adult subjects, time-varying body weight was used for adult volume of distribution terms. Allometric scalars were fixed to 0.75 and 1, respectively, for clearance and volume of distribution-related terms. Effects of food and formulation were evaluated on mean transit time, absorption rate constant (K_a), and relative bioavailability (F_{rel}). Effect of baseline estimated glomerular filtration rate (eGFR) was evaluated on clearance. Effect of baseline age was evaluated on central volume of distribution.

The parameter estimates for the final covariate model are listed in [Table 177](#). The diagnostic plots (observed versus predicted, conditional weighted residuals, normalized prediction distribution errors, and Q-Q plots), for the final covariate model for all data are shown in [Figure 55](#). The visual predictive checks (VPCs) for the final covariate model stratified by phase 3 study, formulation, and disease status are shown in [Figure 56](#). Relationships of ETAs (i.e., random effects) for apparent clearance and select covariates are shown in [Figure 57](#). Forest plot for steady-state AUC is shown in [Figure 58](#).

Table 177. Parameter Estimates (95% CI) for Final PopPK Model

			Estimate	95% CI
Structural model parameters				
NT	$\exp(\theta_1)$	Number of Transit Compartments	8.70	8.30, 9.11
MTT (h)	$\exp(\theta_2)$	Mean Transit Time	2.26	2.08, 2.46
Ka (1/h)	$\exp(\theta_3)$	First Order Absorption Rate Constant	1.26	0.968, 1.64
CL/F (L/h)	$\exp(\theta_4)$	Apparent Clearance	2.56	2.41, 2.71
VC/F (L)	$\exp(\theta_5)$	Apparent Central Volume	18.7	17.1, 20.5
Q1/F (L/h)	$\exp(\theta_6)$	Apparent Intercompartmental Clearance 1	2.28	2.07, 2.52
V2/F (L)	$\exp(\theta_7)$	Apparent Peripheral Compartment 2 Volume	51.1	46.4, 56.2
Q2/F (L/h)	$\exp(\theta_8)$	Apparent Intercompartmental Clearance 2	0.887	0.805, 0.977
V3/F (L)	$\exp(\theta_9)$	Apparent Peripheral Compartment 3 Volume	695	593, 815
F _{rel}	$\exp(\theta_{10})$	Relative Bioavailability of capsule in fed state	1.00	FIXED
Covariate effect parameters				
Capsule _{fasted} ~ MTT	θ_{11}	Fasted capsule effect on MTT	-0.701	-0.996, -0.405
Solution _{fed} ~ MTT	θ_{12}	Fed solution effect on MTT	0.0916	-0.234, 0.417
Capsule _{fasted} ~ F _{rel}	θ_{13}	Fasted capsule effect on F _{rel}	-0.998	-1.21, -0.783
Solution _{fed} ~ F _{rel}	θ_{14}	Fed solution effect on F _{rel}	-0.299	-0.481, -0.117
Capsule _{fasted} ~ Ka	θ_{15}	Fasted capsule effect on Ka	-1.90	-2.50, -1.31
Solution _{fed} ~ Ka	θ_{16}	Fed solution effect on Ka	-0.379	-1.30, 0.538
EGFR ~ CL/F	θ_{17}	eGFR effect on CL/F	-0.158	-0.893, 0.578
AGE ~ CL/F	θ_{18}	Age effect on CL/F	-0.0479	-0.159, 0.0630
AGE ~ VC/F	θ_{19}	Age effect on VC/F	0.105	-0.0394, 0.250

Continued

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Table 177, continued

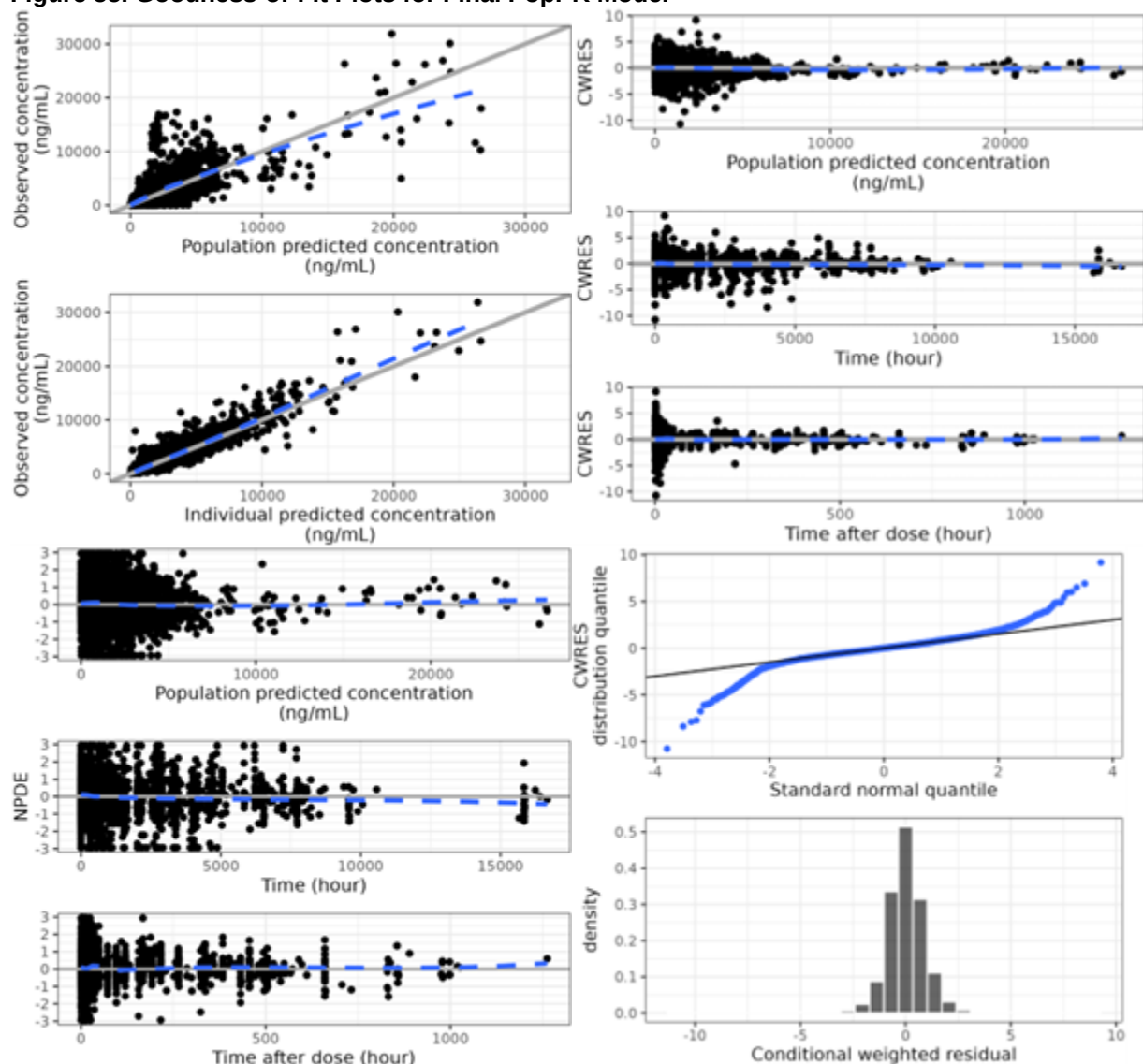
			Estimate	95% CI	Shrinkage (%)
Interindividual variance parameters					
IIV-MTT	$\Omega_{(1,1)}$	Variance of Mean Transit Time	0.257 [CV%=54.2]	0.198, 0.317	21.5
IIV-Ka	$\Omega_{(2,2)}$	Variance of First Order Absorption Rate Constant	0.968 [CV%=128]	0.488, 1.45	43.5
IIV-CL/F	$\Omega_{(3,3)}$	Variance of Apparent Clearance	0.324 [CV%=61.9]	0.177, 0.472	20.5
IIV-VC/F	$\Omega_{(4,4)}$	Variance of Apparent Central Volume	0.198 [CV%=46.8]	0.134, 0.261	33.9
IIV-F _{rel}	$\Omega_{(5,5)}$	Variance of Relative Bioavailability	0.303 [CV%=59.5]	0.197, 0.409	23.0
Interindividual covariance parameters					
Ka-MTT	$\Omega_{(2,1)}$	Covariance of Ka – MTT	0.307 [Corr=0.616]	0.172, 0.443	-
CL/F-MTT	$\Omega_{(3,1)}$	Covariance of CL/F – MTT	0.0710 [Corr=0.246]	0.00885, 0.133	-
CL/F-Ka	$\Omega_{(3,2)}$	Covariance of CL/F – Ka	0.142 [Corr=0.253]	0.00956, 0.274	-
VC/F-MTT	$\Omega_{(4,1)}$	Covariance of VC/F – MTT	0.0163 [Corr=0.0721]	-0.0332, 0.0657	-
VC/F-Ka	$\Omega_{(4,2)}$	Covariance of VC/F – Ka	0.218 [Corr=0.499]	0.0735, 0.363	-
VC/F-CL/F	$\Omega_{(4,3)}$	Covariance of VC/F – CL/F	0.157 [Corr=0.620]	0.0844, 0.230	-
F _{rel} -MTT	$\Omega_{(5,1)}$	Covariance of F _{rel} – MTT	0.0252 [Corr=0.0904]	-0.0351, 0.0856	-
F _{rel} -Ka	$\Omega_{(5,2)}$	Covariance of F _{rel} – Ka	0.151 [Corr=0.280]	0.0136, 0.289	-
F _{rel} -CL/F	$\Omega_{(5,3)}$	Covariance of F _{rel} – CL/F	0.218 [Corr=0.696]	0.0914, 0.345	-
F _{rel} -VC/F	$\Omega_{(5,4)}$	Covariance of F _{rel} – VC/F	0.192 [Corr=0.786]	0.125, 0.260	-
Residual variance					
Residual	$\Sigma_{(1,1)}$	Additive RUV	0.114 [SD=0.337]	0.110, 0.118	6.09

Source: Applicant's popPK report, Tables 5.5 and 5.6, pages 46-47

CI = estimate +/- 1.96 * standard error; CV% of log-normal omegas = sqrt(exp(estimate)-1)*100; CV% of sigma = sqrt(estimate)*100
Parameters estimated in the log-domain were back-transformed.

Abbreviations: CI, confidence interval; CV, coefficient of variation; eGFR, estimated glomerular filtration rate; IIV, interindividual variance; popPK, population pharmacokinetic(s); RUV, residual unexplained variability; SD, standard deviation

Figure 55. Goodness-of-Fit Plots for Final PopPK Model

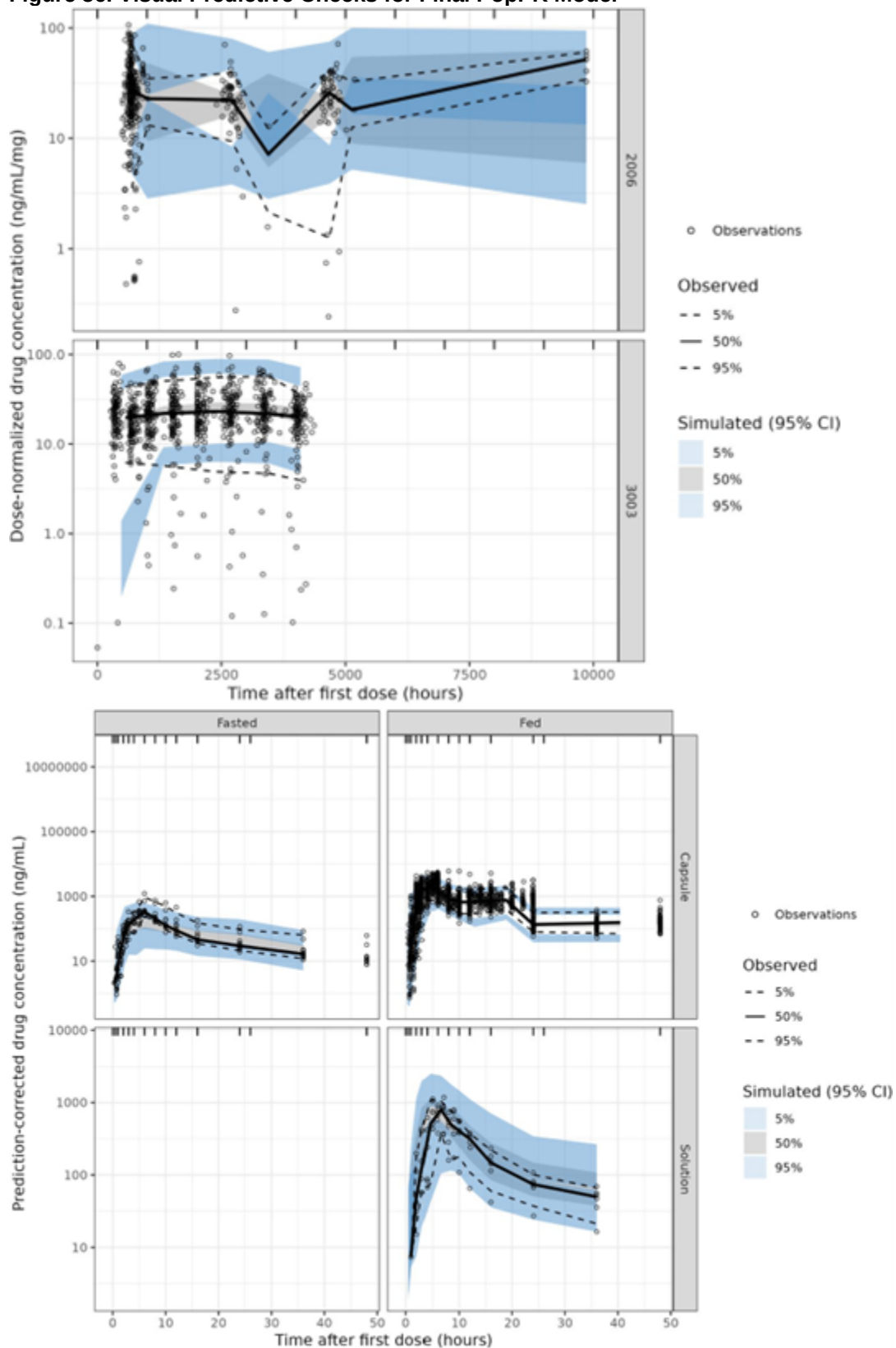


Source: Applicant's popPK report, Figures A.61, A.62, A.63, A.64, pages 117-120

Observed values are indicated by black dots; the line of identity (solid grey) is included as a reference $x = y$ for observed vs. predicted plots; the solid horizontal grey line indicates residuals = 0; the dashed blue line represents a LOESS smooth through the data; density plot shows the density of the CWRES

Abbreviations: CWRES, conditional weighted residuals; NPDE, normalized prediction distribution errors; LOESS, locally weighted scatterplot smoothing; popPK, population pharmacokinetic(s)

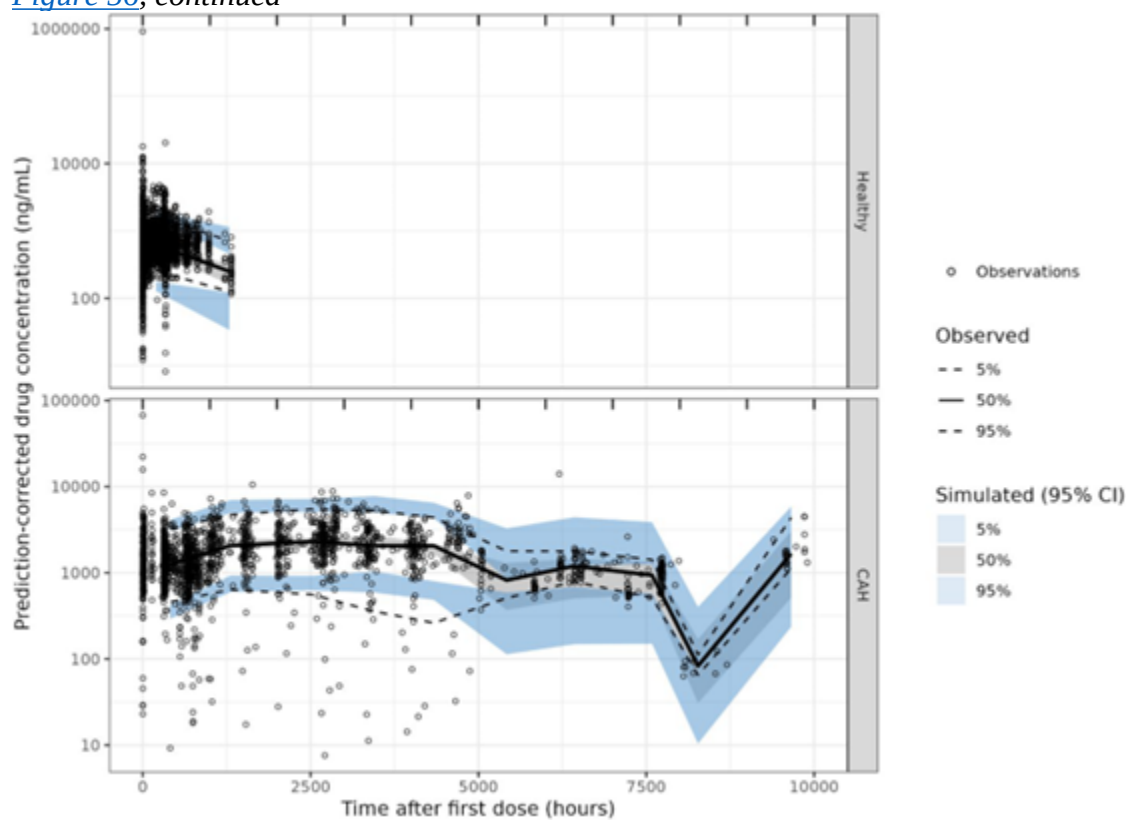
Figure 56. Visual Predictive Checks for Final PopPK Model



Continued

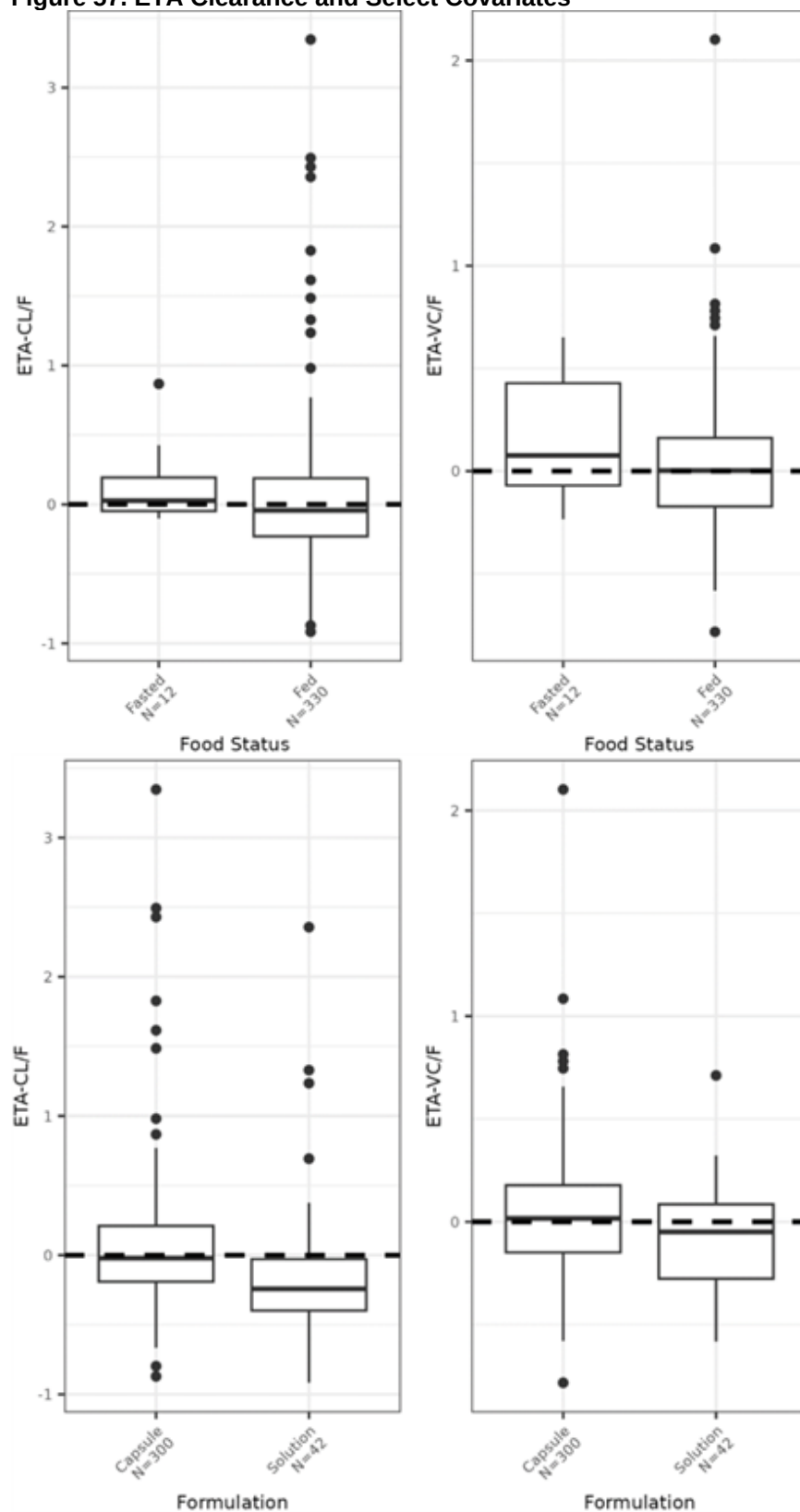
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[Figure 56](#), continued



Source: Applicant's popPK report, Figures A.107, A.111, A.112, pages 163, 167, 168
Abbreviations: CI, confidence interval; popPK, population pharmacokinetic(s)

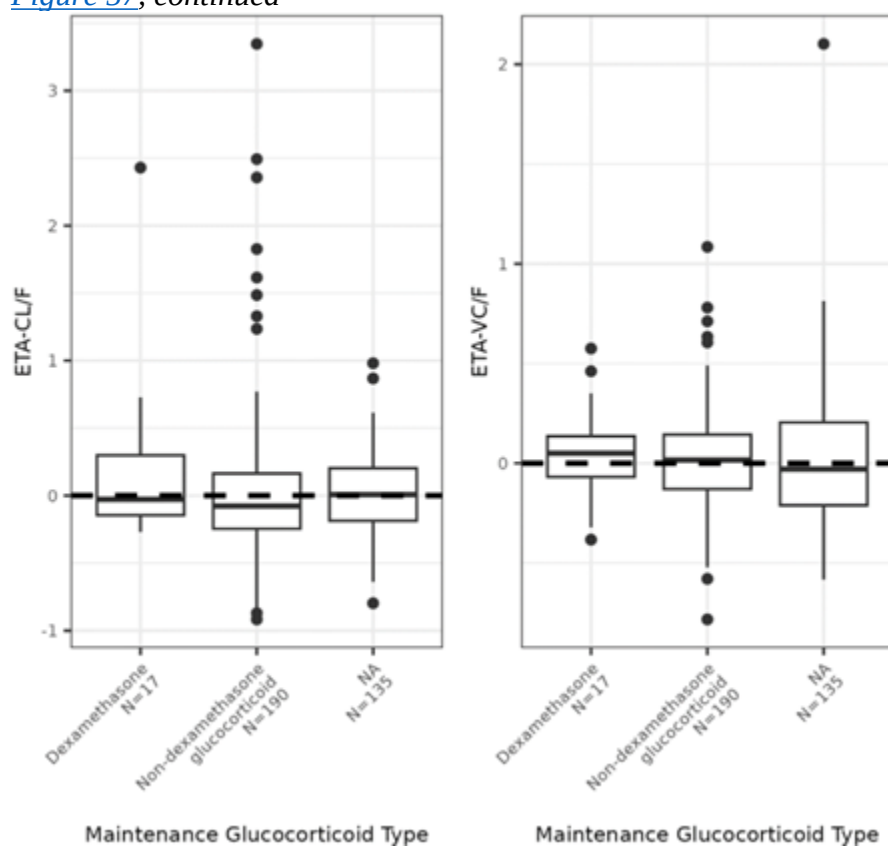
Figure 57. ETA Clearance and Select Covariates



Continued

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

[Figure 57](#), continued

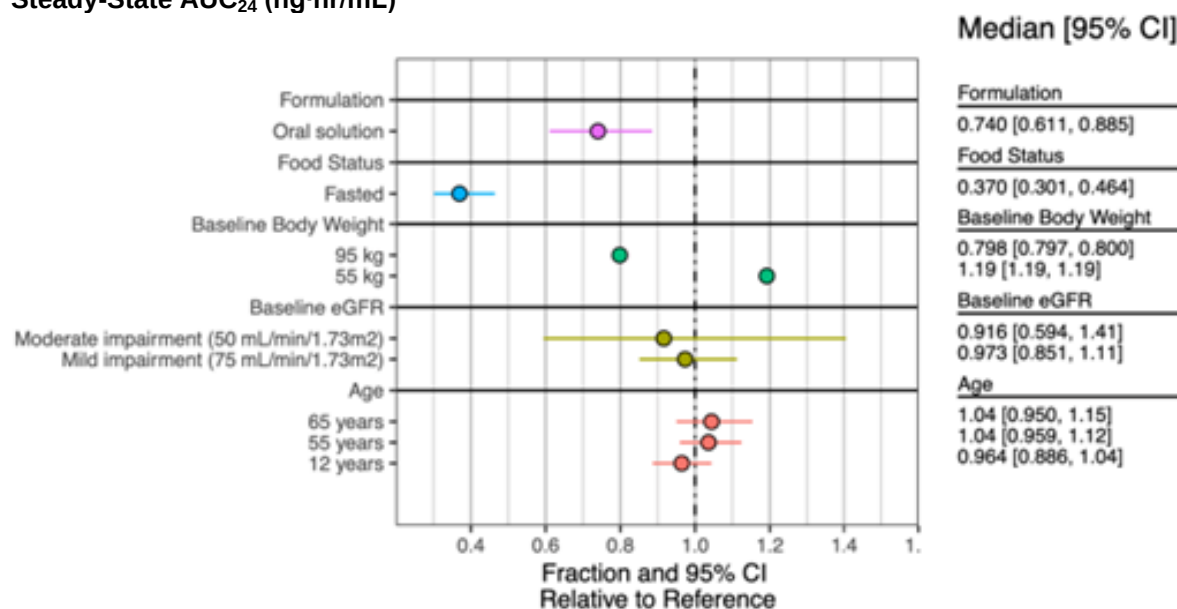


Source: Applicant's popPK report, Figures A.75, A.78, A.84, pages 131, 134, 140

Median values are designated by a solid line in the center of the box; boxes indicate the interquartile range (IQR) with whiskers extending to 1.5*IQR; a dashed black line at y =0 is included as a reference

Abbreviations: ETA, random effects; CL/F, apparent clearance; NA, not applicable; N, sample size of subgroup; popPK, population pharmacokinetics

**Figure 58. Forest Plots of Covariate Effects on Crinecerfont Exposure
Steady-State AUC₂₄ (ng·hr/mL)**



Source: Applicant's popPK report, Figure 1.1, page 18

Reference subject of 70 kg and 26 years of age with eGFR of 90 mL/min/1.73 m² taking crinecerfont capsules in fed state
Abbreviations: AUC, area under the concentration-time curve; CI, confidence interval; popPK, population pharmacokinetic(s)

The reviewer was able to reproduce and verify the Applicant's final popPK model, and no discordance was identified. The model parameters were estimated with reasonable precision based on the relative standard errors (RSEs) and the 95% CIs (as shown above). The highest RSEs for the key PK parameters were 51.2% and 29.4% for K_a and Q_2 , respectively, and all other RSEs were below 5%. The shrinkages were generally acceptable in supporting simulation for dose selection in another population (between 20.5% to 33.9% except for K_a at 43.5%). Given the populations studied (adults and pediatric subjects), formulation differences, and food effect (fed and fasted states), the relatively higher variabilities around K_a and associated interindividual variability are expected. Based on the observed versus predicted data scatter plots, the data points are randomly scattered around the line of unity with no significant trend identified. The conditional weighted residuals (CWRES) and normalized prediction distribution errors (NPDE) plots also demonstrate no bias or misspecification of the final model.

Additionally, the VPCs and select ETA plots also support that the popPK model adequately captures the central tendency of crinecerfont pharmacokinetics. For additional model diagnostic plots, such as random effects versus covariates, refer to the Applicant's popPK report. Overall, the popPK model is adequate in describing crinecerfont pharmacokinetics in the target adult and pediatric patient populations, in simulation for dose selection in the 10 to <20 kg pediatric group, and in deriving phase 3 individual PK exposure metrics for E-R safety and efficacy analyses.

(b) (4)

20.5.5. Comparison of Adult and Pediatric Exposures

Based on clinical benefits achieved with crinecerfont exposures (i.e., AUC₂₄) corresponding to 200 mg once daily (Study TDR10671) or 100 mg bid (Trial NBI-74788-CAH2001), the Applicant selected the 100 mg bid dosing regimen because of the potential to produce sustained CRF antagonist activity over the entire day (refer to Section 12.1.1). For selection of the dosing regimen for pediatric patients by weight bands (10 to <20 kg, 20 to <55 kg, and ≥55 kg, corresponding to regimens of 25 mg solution bid, 50 mg solution bid, and 100 mg capsule bid), the Applicant used exposure matching to the adult subjects. To match to the adult exposures of 100 mg bid, simulations were performed incorporating allometry for pediatric subjects with CAH using the final popPK model.

A total of 500 virtual subjects were simulated for each dose level and weight band. Ages and weight were sampled from the National Health and Nutrition Examination Survey (NHANES) dataset, and crinecerfont doses were simulated for the fed state. Simulated exposures of steady-state AUC₂₄ were compared between pediatric subjects and adult subjects. For the simulation, PK parameters were fixed to the final popPK model values. Of note, the clinical studies did not include pediatric subjects under 20 kg. Covariates sampled from the NHANES dataset provided virtual pediatric subjects of 10 to <20 kg. Simulated steady-state AUCs are summarized in Table 178 and Table 179 and are illustrated in Figure 59 by dosing groups and formulation.

Table 178. Summary of Steady-State 24-Hour AUCs by Groups

Group	Formulation	N	AUC _{24,ss} (ng·hr/mL)		
			Median	5 th Percentile	95 th Percentile
Ped 10 to <20 kg (25 mg bid)	Solution	500	41662	19388	85417
Ped 20 to <55 kg (50 mg bid)	Solution	500	45679	21716	105680
Ped ≥55 kg (100 mg bid)	Capsule	500	74800	35310	158180
Adult (100 mg bid)	Capsule	500	74484	32859	159100

Source: Applicant's popPK report, Table 5.7, page 49

Abbreviations: AUC, area under the concentration-time curve; AUC_{24,ss}, AUC over 24 hours at steady state; bid, twice daily; N, sample size; ped, pediatric; popPK, population pharmacokinetic(s)

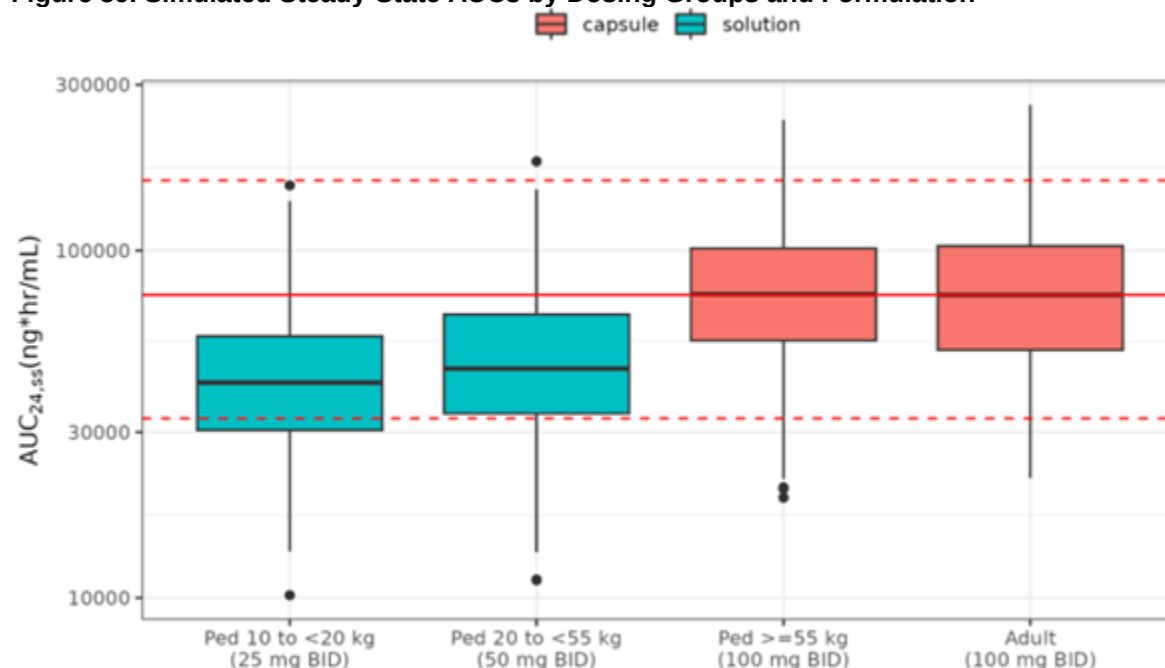
Table 179. Summary of Percent of Virtual Subjects With 24-Hour AUCs Overlapping With Adult 24-Hour AUC 90% PI

Group	Formulation	Total N	N With AUC _{24,ss} in Adult 90% PI	Percent With AUC _{24,ss} in Adult 90% PI
Ped 10 to <20 kg (25 mg bid)	Solution	500	342	68.4
Ped 20 to <55 kg (50 mg bid)	Solution	500	384	76.8
Ped ≥55 kg (100 mg bid)	Capsule	500	458	91.6

Source: Applicant's popPK report, Table 5.8, page 50

Abbreviations: AUC, area under the concentration-time curve; AUC_{24,ss}, AUC over 24 hours at steady state; bid, twice daily; N, sample size; ped, pediatric; PI, prediction interval; popPK, population pharmacokinetic(s)

Figure 59. Simulated Steady-State AUCs by Dosing Groups and Formulation



Source: Applicant's popPK report, Figure 1.2, page 19

Dashed red lines represent the 5th and 95th percentiles of the adult 100 mg bid 24-hr AUC at steady-state; solid red line represents the median; box represents the interquartile range (IQR), with the median indicated by the horizontal black line within the box; whiskers represent the range from quartile 1 minus 1.5*IQR to quartile 3 plus 1.5*IQR; outliers are indicated by black points
Abbreviations: AUC, area under the concentration-time curve; popPK, population pharmacokinetic(s); bid, twice daily; Ped, pediatric

The simulation results demonstrated that pediatric subjects weighing ≥ 55 kg and 20 to <55 kg have overlapping exposures (i.e., AUC at steady state) when compared to the adult exposures, resulting in 91.6% and 76.8% of pediatric subjects within the 90% prediction interval, respectively. For pediatric subjects weighing 10 to <20 kg, the percentage of simulated subjects falling within the 90% prediction interval of the adult exposure was numerically lower (68.4%) than those of the other two pediatric subgroups. Additionally, the median AUCs of the two lowest pediatric weight bands were lower than the 50th percentile of the adult AUC.

To further assess the appropriateness of the 25 mg bid dosing in the absence of studying the 10 to <20 kg population (i.e., no PK or clinical outcomes data), the following key points were considered:

- Based on the disease state, pathophysiology, and current standard of care, pediatric patients down to 4 years of age with CAH are likely to fall under the 20 to <55 kg group (see Section [12.3.1](#)).
- PK data and clinical outcomes data were available from pediatric subjects weighing 20 to <55 kg in the phase 3 clinical trial ([Table 175](#)), and this pediatric subgroup is more physiologically similar when compared to pediatric patients weighing 10 to <20 kg regarding physiology, disease state, disease progression, and expected efficacy response for CAH (based on the indicated age cut-off).
- Efficacy outcomes of the pediatric subjects weighing 20 to <55 kg are considered acceptable per the clinical review team assessment (see Section [12.3.1](#)).
- The relatively higher exposure in adult subjects serve as the safety exposure coverage.

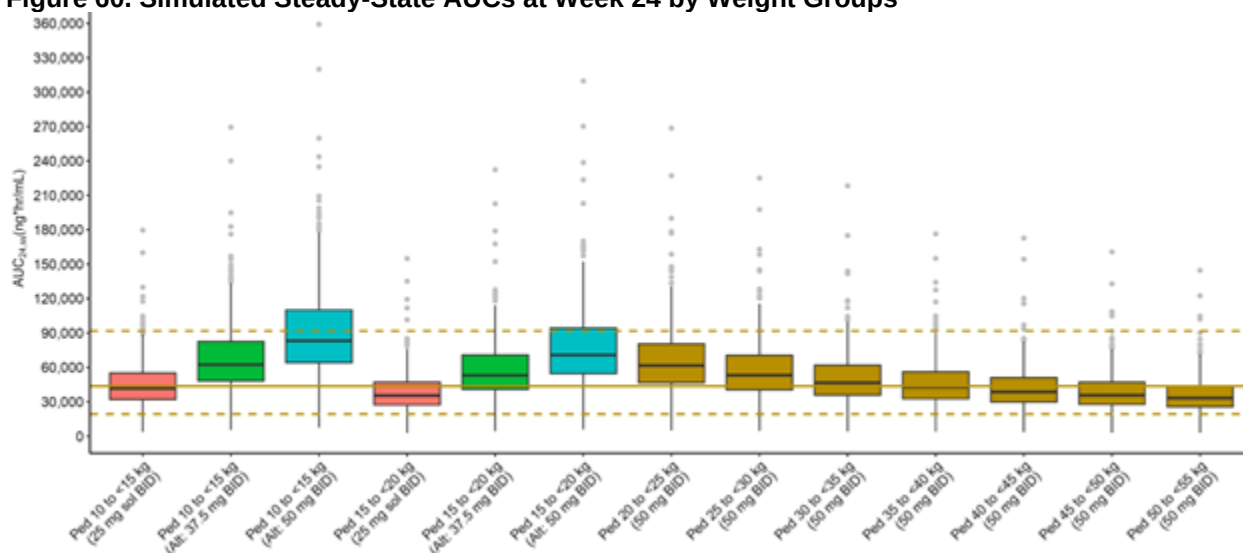
Therefore, the pediatric subgroup of 20 to <55 kg is an acceptable efficacy reference group for exposure matching for the 10 to <20 kg group.

Further simulations of alternative regimens were conducted by the reviewer to support the 25 mg bid regimen. For the virtual population, a total of 9500 subjects were generated using the NHANES database across all 4 groups as shown below. Specifically, 1000 and 3500 subjects were allocated to the 10 to <20 kg group and 20 to <55 kg group, respectively, with 500 virtual pediatric subjects allocated for each subgroup at 5-kg increments. In the reviewer's analysis, two adjustments were made to reflect the indication for crinecerfont in this NDA: (1) the minimum age was raised to 4 years, and (2) the upper bound of the adult body weight was capped at 155 kg, which is approximately one standard deviation (of the body weight distribution of the overall PK population) above the highest body weight studied in the PK population.

The 25 mg bid, 37.5 mg bid, and 50 mg bid dosages of the solution formulation were simulated for the 10 to <20 kg group. The proposed dosage of 50 mg bid was simulated for the 20 to <55 kg group.

As shown in [Figure 60](#) and [Figure 61](#), the simulated regimens of 37.5 mg bid and 50 mg bid for the 10 to <20 kg group had improved AUC and C_{max} relative to those of the reference population of 20 to <55 kg; however, relatively higher proportions of the simulated subjects were also projected to have exposures above the 95th percentile of the reference exposures. Therefore, 25 mg bid for the 10 to <20 kg subgroup is expected to produce similar exposures to those of 50 mg bid for the 20 to <55 kg subgroup, and because a high proportion of subjects weighing 10 to <20 kg is expected to have exposures within the adult exposure, the exposures of the proposed 25 mg bid in 10 to <25 kg subgroup is expected to be safe and effective.

Figure 60. Simulated Steady-State AUCs at Week 24 by Weight Groups

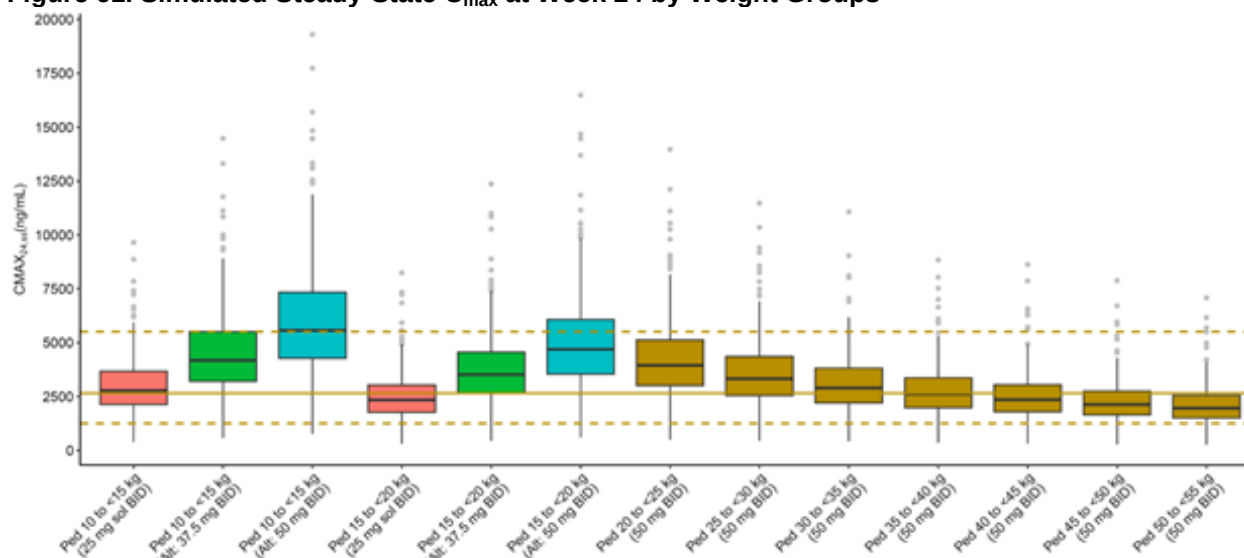


Source: Reviewer's analysis

Dashed red lines represent the 5th and 95th percentiles of the pediatric 24-hr AUC at steady-state and solid red line represents the median for subgroup of 20 to <55 kg; box represents the interquartile range (IQR), with the median indicated by the horizontal black line within the box; whiskers represent the range from 25th percentile minus 1.5*IQR to 75th percentile plus 1.5*IQR; outliers are indicated by grey points

Abbreviations: Ped, pediatric; Alt, alternative dosing; AUC, area under the concentration-time curve; bid, twice daily

Figure 61. Simulated Steady-State C_{max} at Week 24 by Weight Groups



Source: reviewer's analysis

Dashed red lines represent the 5th and 95th percentiles of the pediatric 24-hr C_{max} at steady-state and solid red line represents the median for subgroup of 20 to <55 kg; box represents the interquartile range (IQR), with the median indicated by the horizontal black line within the box; whiskers represent the range from 25th percentile minus 1.5*IQR to 75th percentile plus 1.5*IQR; outliers are indicated by grey points

Abbreviations: Ped, pediatric; Alt, alternative dosing; C_{max} , maximum observed plasma concentration; bid, twice daily

20.5.6. E-R Analysis

Using data from the phase 3 studies in adult (CAH3003) and pediatric (CAH2006) subjects with CAH, E-R analyses were conducted independently in each population to characterize the relationship between plasma exposure and clinical endpoints and to support evidence of effectiveness of the proposed doses for adult and pediatric patients with CAH. The Applicant's objectives of the E-R analyses were to:

- Develop an exposure-efficacy model for percent CFB in daily GC dose while maintaining adequate control of androgen levels at Week 24 (CAH3003) and Week 28 (CAH2006) in adult and pediatric subjects with CAH, respectively
- Develop an exposure-efficacy model for the achievement of reduction in GC daily dose to physiologic levels (≤ 11 mg/m²/day hydrocortisone equivalent adjusted for body surface area [BSA]) while maintaining adequate control of androgen levels at Week 24 (CAH3003) and Week 28 (CAH2006) in adult and pediatric subjects with CAH, respectively
- Develop an exposure-efficacy model for change from baseline in serum A4 (i.e., androstenedione) prior to morning GC dose at Week 4 while subjects were on a stable background GC daily dose in adult and pediatric subjects with CAH
- Develop an exposure-safety model for a safety endpoint in adult and pediatric subjects with CAH, if deemed necessary
- Evaluate the effects of select covariates of interest on E-R relationships
- Compare the E-R relationships between adult and pediatric subjects

Refer to Section 20.2 for primary and secondary endpoints for Trial CAH3003 and Trial CAH2006. Each phase 3 study was used for adult and pediatric E-R analysis, respectively, and the studies are summarized in Table 180. Exposure metrics were generated based on the final popPK model structure using the individual PK parameter, actual dosing record, and covariates for individuals. Base E-R model structures (i.e., maximum drug effect [E_{max}] model and logistic regression) are shown in Equation 1 and Equation 2, respectively, to describe the efficacy endpoints for both the adult and pediatric E-R analyses. Additionally, select covariates were adjusted for in the E-R models as summarized in Table 181. Model evaluation includes model fit adequacy, parameter precision, model stability, significant reductions in objective function value between hierarchical models, and standard goodness-of-fit plots.

Table 180. Clinical Study Summary and Endpoints

Study	Title	Number of Subjects	Dose Levels	Key Endpoint Assessments
CAH3003 (phase 3)	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Crinecerfont (NBI-74788) in Adult Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment	182	100 mg bid or placebo	Serum A4: pre-morning glucocorticoid dose on Week 4 Glucocorticoid daily dose: Week 24
CAH2006 (phase 3)	A Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Crinecerfont (NBI-74788) in Pediatric Subjects with Classic Congenital Adrenal Hyperplasia, Followed by Open-Label Treatment	103	25 mg bid via oral solution for subjects 10 to <20 kg 50 mg bid via oral solution for subjects 20 to <55 mg 100 mg bid via oral capsules for subjects ≥55 kg Respective matching placebo	Serum A4: pre-morning glucocorticoid dose on Week 4 Glucocorticoid daily dose: Week 28

Source: Applicant's E-R report, Table 3.1, page 35
Abbreviations: A4, androstenedione; bid, twice daily

Equation 1. Percent CFB in GC Daily Dose

$$R_i = INT_i + \frac{E_{max,i} \cdot Exp_i^{Y_i}}{EC_{50,i} + Exp_i^{Y_i}}$$

Source: Applicant's E-R report, Equation 4.1, page 38
Abbreviations: CFB, change from baseline; E-R, exposure-response; EC_{50,i}, exposure to reach half of the maximal effect; E_{max,i}, maximal effect of exposure on change in GC daily dose; Exp_i, crinecerfont exposure; GC, glucocorticoid; INT_i, percentage of CFB in GC daily dose at Week 24 without crinecerfont exposure (i.e., intercept) for subject i; Y_i, Hill coefficient

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Equation 2. Achievement of GC Daily Dose at Physiologic Levels

$$\text{logit}(P_{i,\text{response}}) = \log\left(\frac{P_{i,\text{response}}}{1-P_{i,\text{response}}}\right) = \text{INT}_i + \beta_i \cdot \text{Exp}_i$$

Source: Applicant's E-R report, Equation 4.2, page 39

Abbreviations: β_i , effective of crinecerfont exposure; E-R, exposure-response; GC, glucocorticoid; INT_i , intercept; $P_{i,\text{response}}$, the probability of subject i achieving the response

Table 181. Covariates Evaluated for E-R Analyses

Response	Covariates
Efficacy (percent change from baseline glucocorticoid daily dose, achievement of glucocorticoid daily dose at physiologic levels, change from baseline serum A4)	Age, body weight, sex, race/ethnicity, glucocorticoid type (dexamethasone versus non-dexamethasone), baseline glucocorticoid daily dose, baseline serum A4

Source: Applicant's E-R report, Table 4.1, page 41

Abbreviations: A4, androstenedione; E-R, exposure-response

20.5.6.1. Adult E-R Analysis

20.5.6.1.1. Serum A4 Change From Baseline

Table 182. Serum A4 Final E-R Model (Adult)

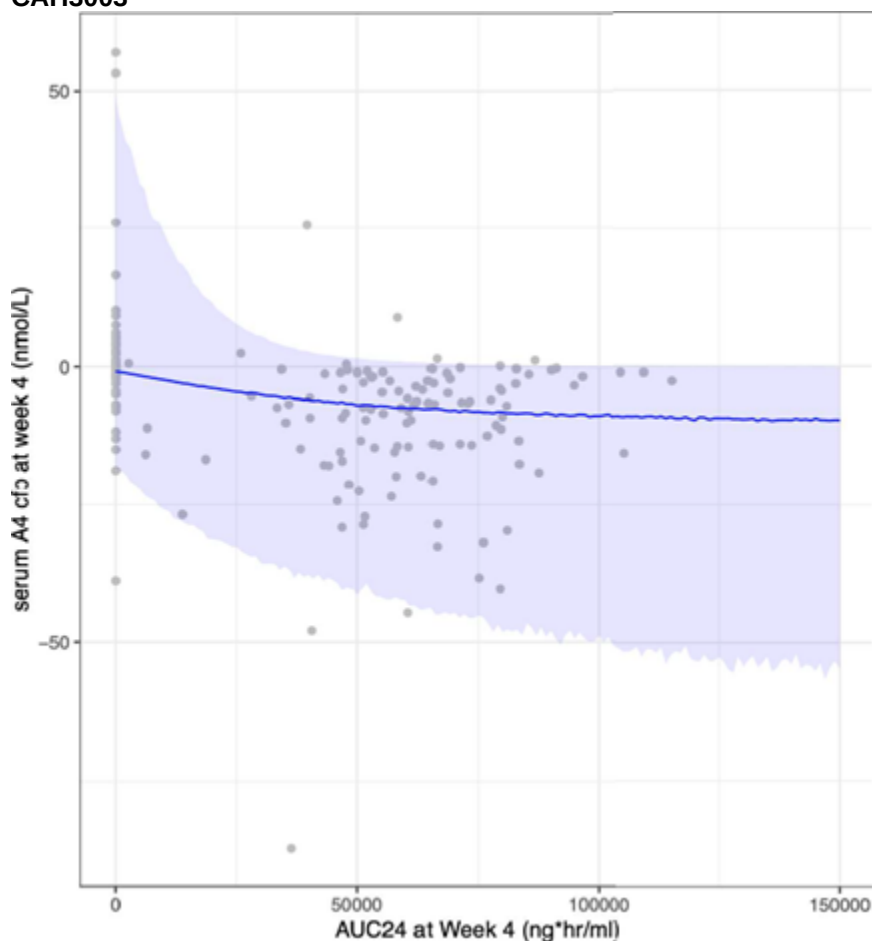
			Estimate	95% CI
Structural model parameters				
Emax	$\exp(\theta_1)/(1 + \exp(\theta_1))$	Maximum effect (proportional change in A4) attributable to the drug	0.981	0.817, 0.998
EC50, ng*hr/mL	$\exp(\theta_2)$	AUC24 which produces half of Emax	26300	17800, 38900
INT	θ_3	Intercept	-0.122	-0.314, 0.0702
Covariate effect parameters				
INT~AGE	θ_4	Effect of age on INT	-0.00841	-0.0188, 0.00202
INT~LOG(BLA4)	θ_5	Effect of log baseline A4 on INT	0.103	-0.0278, 0.234
INT~SEX	θ_6	Effect of sex on INT	0.0464	-0.160, 0.253
INT~BWT	θ_7	Effect of body weight on INT	-0.00341	-0.00915, 0.00233
Emax~LOG(BLA4)	θ_8	Effect of log baseline A4 on Emax	3.49	0.835, 6.14
Residual variance				
Residual	$\Sigma_{(1,1)}$	Additive RUV	0.443 [SD=0.666]	0.350, 0.537

Source: Applicant's E-R report, Table 5.7, page 52

Parameters in the log domain were back-transformed.

Abbreviations: AUC24, area under the plasma concentration-time curve over 24 hours; A4, androstenedione; CI, confidence interval; E-R, exposure-response; RUV, residual unexplained variability; SD, standard deviation; SE, standard error

Figure 62. Simulated Adult Serum A4 CFB at Week 4 vs. Crinecerfont AUC₂₄ at Week 4, Trial CAH3003



Source: Applicant's E-R report, Figure 13.2, page 97

Grey points represent the observed data; blue line is the model-predicted median; shaded area, 90% CI
Abbreviations: CI, confidence interval; E-R, exposure-response; AUC, area under the concentration-time curve; A4, androstenedione; cfb, change from baseline

In the Applicant's E-R model for serum A4, parameter precision of fixed effects appears reasonable based on the 95% CI. Null effect is included in the 95% CI of the intercept estimate and 95% CI of the covariate effects on the intercept, indicating that impacts from those covariates were minimal (on the intercept). Based on the final model predictions, the exposure-response relationship is relatively flat within the studied crinecerfont exposure range.

20.5.6.1.2. GC Percent Change From Baseline

Table 183. Percent Glucocorticoid CFB Final E-R Model (Adult)

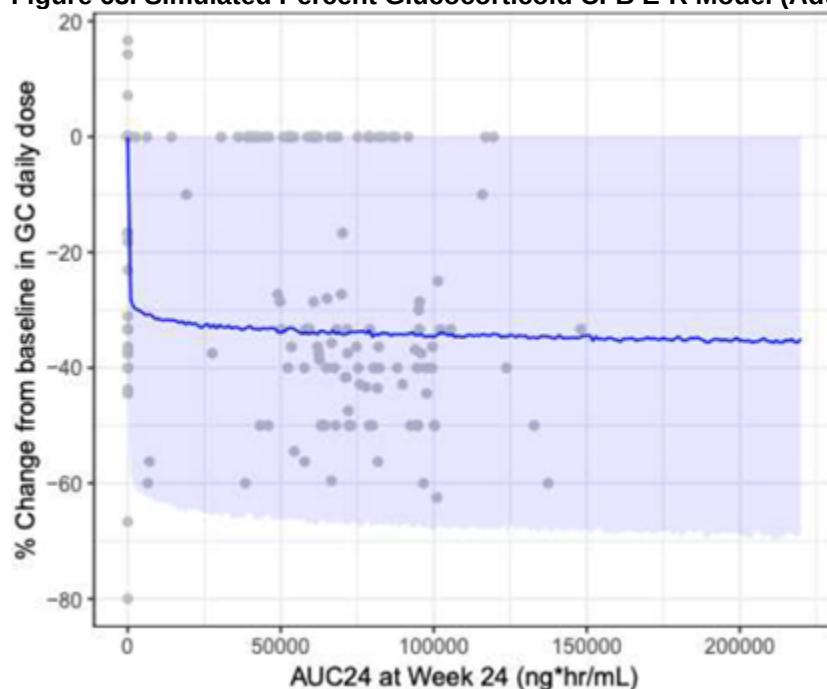
			Estimate	95% CI
Structural model parameters				
INT	θ_1	Intercept	-25.1	-31.9, -18.3
BETA (%*mL/(ng*hr))	θ_2	Log-linear slope of drug effect (AUC24)	-1.31	-1.95, -0.660
$P_{tx,change=0}$	$\exp(\theta_3)/(1 + \exp(\theta_3))$	Probability of treatment group having zero change	0.314	0.236, 0.403
$P_{plb,change=0}$	$\exp(\theta_4)/(1 + \exp(\theta_4))$	Probability of placebo group having zero change	0.596	0.465, 0.715
Covariate effect parameters				
INT ~ AGE	θ_5	Effect of age on INT	-0.170	-0.412, 0.0720
INT ~ BLGC	θ_6	Effect of baseline GC dose on INT	-1.79	-2.25, -1.33
INT ~ SEX	θ_7	Effect of sex on INT	1.70	-2.27, 5.66
INT ~ BWT	θ_8	Effect of body weight on INT	0.0924	-0.0428, 0.228
BETA ~ BLGC	θ_9	Effect of baseline GC dose on BETA	-0.0980	-0.171, -0.0246
Residual variance				
Residual	$\Sigma_{(1,1)}$	Additive RUV	107 [SD=10.3]	53.8, 160

Source: Applicant's E-R report, Table 6.4, page 6

Parameters in the log domain were back-transformed.

Abbreviations: AUC24, area under the plasma concentration-time curve over 24 hours; BLGC, baseline GC; CFB, change from baseline; CI, confidence interval; E-R, exposure-response; GC, glucocorticoid; RUV, residual unexplained variability; SD, standard deviation; SE, standard error

Figure 63. Simulated Percent Glucocorticoid CFB E-R Model (Adult), Trial CAH3003



Source: Applicant's E-R report, Figure 13.5, page 102

Grey points represent the observed data; blue line is the model-predicted median; shaded area, 90% CI

Abbreviations: CI, confidence interval; E-R, exposure-response; AUC, area under the concentration-time curve; A4, androstenedione; cfb, change from baseline; GC, glucocorticoid

In the Applicant's E-R model for percent GC reduction at Week 24 from baseline, the parameter precision of fixed effects appears reasonable based on the 95% CI. Null effect is contained within the 95% CI of the age, sex, and body weight effect on intercept, indicating minimal impact. Based on the final model predictions, the exposure-response relationship is relatively flat within the studied crinecerfont exposure range. Of note, subjects who received crinecerfont and had GC reduction yet failed to maintain A4 control were imputed to have 0% change from baseline (see Section [12.2.2.4.2.1](#)).

20.5.6.1.3. GC Daily Dose Reduction to Physiologic Levels at Week 24

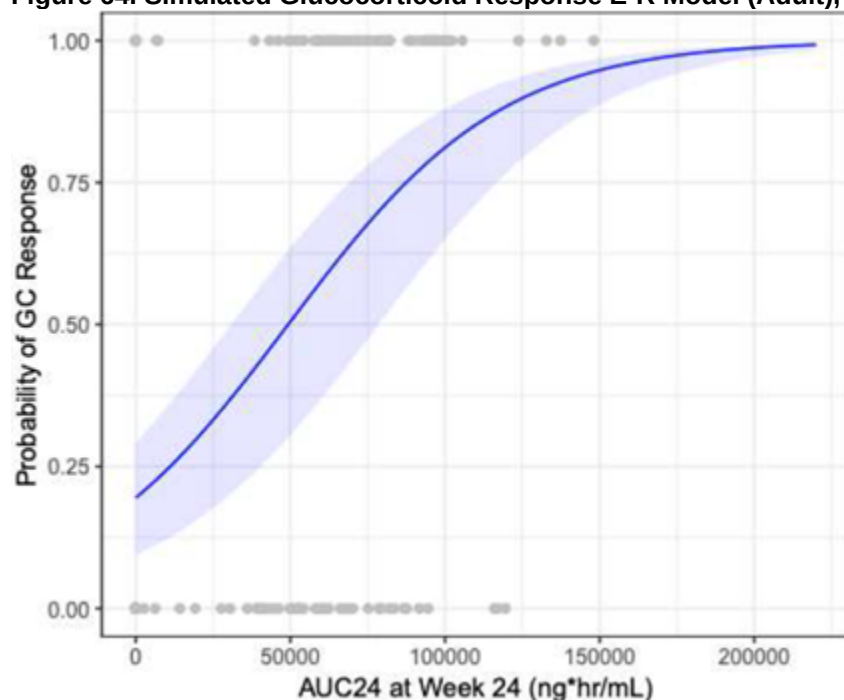
Table 184. Glucocorticoid Response E-R Model (Adult)

			Estimate	95% CI
Structural model parameters				
INT	θ_1	Intercept	-1.38	-2.06, -0.686
BETA (mL/(ng*hr))	θ_2	Linear slope of drug effect (AUC24)	2.88e-05	1.91e-05, 3.85e-05
Covariate effect parameters				
INT ~ AGE	θ_3	Effect of age on INT	0.0193	-0.0169, 0.0555
INT ~ BLGC	θ_4	Effect of baseline GC dose on INT	-0.0603	-0.144, 0.0236
INT ~ SEX	θ_5	Effect of sex on INT	-0.0278	-0.746, 0.690
INT ~ BWT	θ_6	Effect of body weight on INT	-0.0101	-0.0305, 0.0103

Source: Applicant's E-R report, Table 7.3, page 67

Abbreviations: AUC24, area under the plasma concentration-time curve over 24 hours; BLGC, baseline GC; CI, confidence interval; E-R, exposure-response; GC, glucocorticoid; SD, standard deviation; SE, standard error

Figure 64. Simulated Glucocorticoid Response E-R Model (Adult), Trial CAH3003



Source: Applicant's E-R report, Figure 13.5, page 102

Grey points represent the observed data; blue line is the model-predicted median; shaded area, 90% CI

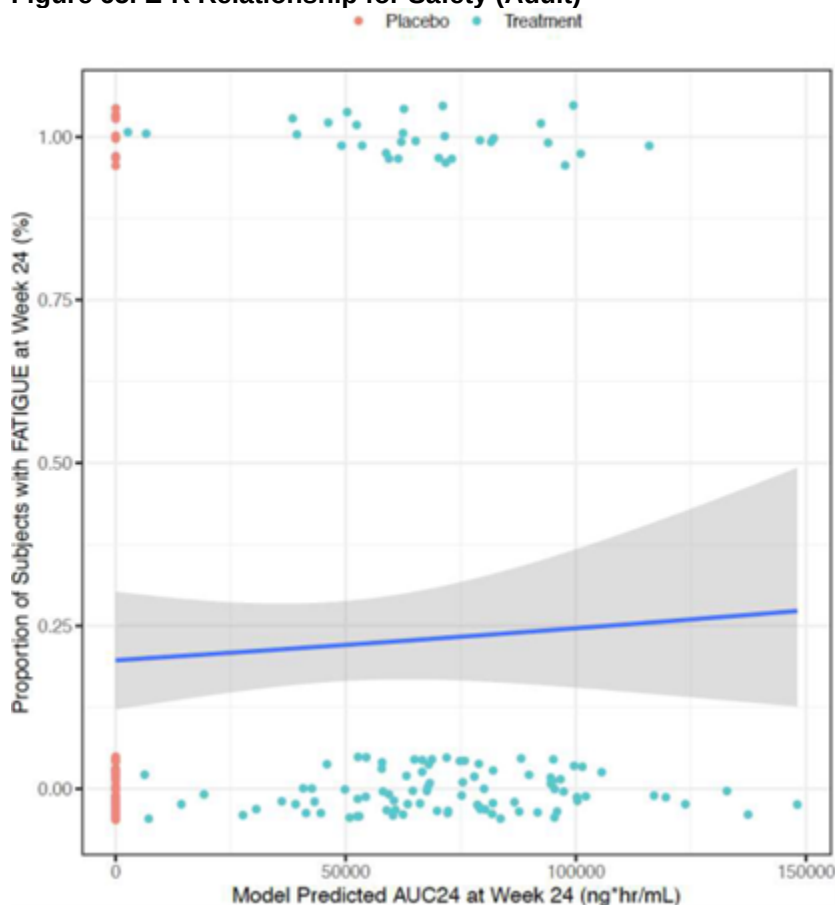
Abbreviations: CI, confidence interval; E-R, exposure-response; AUC, area under the concentration-time curve; GC, glucocorticoid

In the Applicant's E-R model for GC response at Week 24 from baseline, the parameter precision of fixed effects appears reasonable based on the 95% CI. Null effect is contained within the 95% CI of age, sex, body weight, and baseline GC dose effect on intercept, indicating minimal impact. Based on the final model predictions, the exposure-response relationship suggests that the probability of achieving a GC response (i.e., GC dose at physiologic levels) increases as crinecerfont exposure increases (within the range of studied exposure); however, the 95% CIs of the beta slope are numerically small (0.0000191 to 0.0000385) and approaching zero, suggesting that the odds ratio is close to 1 and that other factors may also be driving the probability of GC response. Overall, the results of this E-R analysis should be interpreted with caution.

20.5.6.1.4. Safety

In the adult study, TEAEs that occurred with at least 5% greater incidence in the crinecerfont arm were fatigue (24.6% crinecerfont; 15.3% placebo), coronavirus infection (13.9%; 8.5%), and arthralgia (7.4%; 0%). Fatigue had the highest reported frequency in the crinecerfont arm and was, therefore, selected as the AE for exploratory E-R analysis.

Figure 65. E-R Relationship for Safety (Adult)



Source: Applicant's E-R report, Figure A.39, page 156

Solid circles represent the data points; the solid blue line represents the LOESS smooth trend line through the data

Abbreviations: AUC, area under the concentration-time curve; E-R, exposure-response; LOESS, locally weighted scatterplot smoothing

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The reviewer agrees with the Applicant's statement that there is no apparent relationship between crinecerfont AUC and proportion of subjects with fatigue across the studied exposure range. Additionally, no apparent relationships were noted for $C_{\max}$, $C_{\min}$ (minimum concentration), and C_{avg} (average concentration) at Week 24 versus fatigue within the respective exposure range (refer to Applicant's E-R report, Section 8).

Overall, the results from the exposure-efficacy and exploratory exposure-safety analyses support the proposed doses for adults with CAH in achieving clinical benefits and support that no alternative dosing approaches are needed.

20.5.6.2. Pediatric E-R Analysis

20.5.6.2.1. Serum A4 Change From Baseline

Table 185. Serum A4 Final E-R Model (Pediatric)

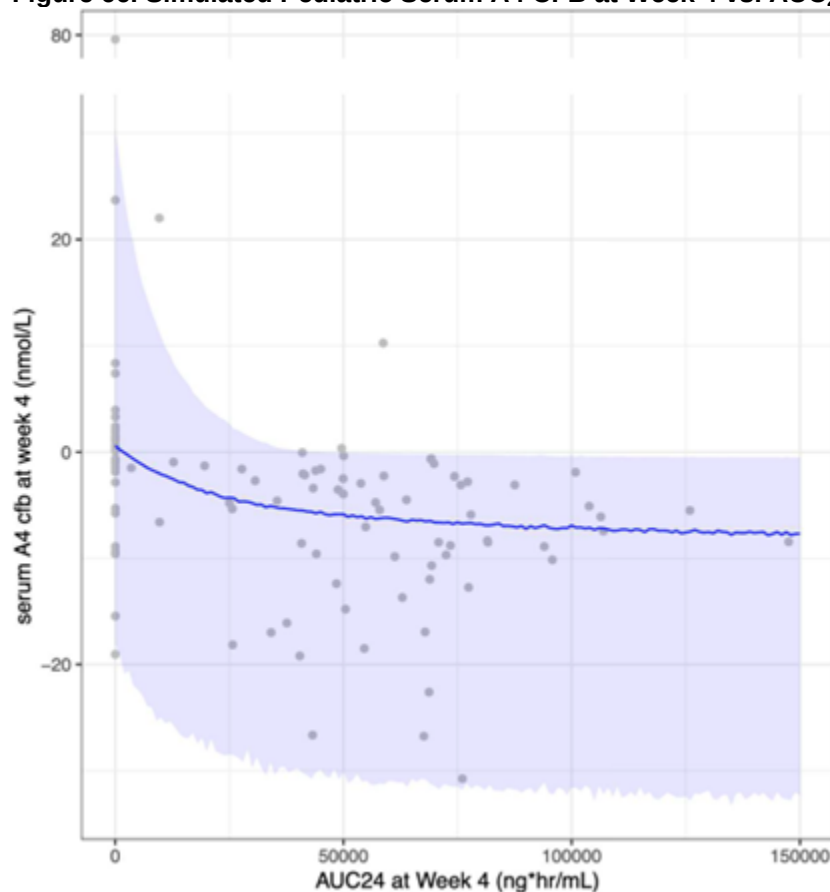
			Estimate	95% CI
Structural model parameters				
Emax	$\exp(\theta_1)/(1 + \exp(\theta_1))$	Maximum effect (proportional change in A4) attributable to the drug	0.903	0.762, 0.964
EC50, ng*hr/mL	$\exp(\theta_2)$	AUC24 which produces half of Emax	10500	5770, 19300
INT	θ_3	Intercept	-0.0446	-0.280, 0.191
Covariate effect parameters				
INT~AGE	θ_4	Effect of age on INT	0.100	0.0528, 0.148
INT~LOG(BLA4)	θ_5	Effect of log baseline A4 on INT	-0.362	-0.512, -0.211
INT~SEX	θ_6	Effect of sex on INT	0.247	0.00614, 0.488
Emax~LOG(BLA4)	θ_8	Effect of log baseline A4 on Emax	-1.20	-2.14, -0.250
Residual variance				
Residual	$\Sigma_{(1,1)}$	Additive RUV	0.379 [SD=0.616]	0.275, 0.484

Source: Applicant's E-R report, Table 9.7, page 77

Parameters in the log domain were back-transformed.

Abbreviations: AUC24, area under the plasma concentration-time curve over 24 hours; A4, androstenedione; CI, confidence interval; E-R, exposure-response; RUV, residual unexplained variability; SD, standard deviation; SE, standard error

Figure 66. Simulated Pediatric Serum A4 CFB at Week 4 vs. AUC₂₄ at Week 4, Trial CAH2006



Source: Applicant's E-R report, Figure 13.3, page 102

Grey points represent the observed data; blue line is the model-predicted median; shaded area, 90% CI

Abbreviations: CI, confidence interval; E-R, exposure-response; AUC, area under the concentration-time curve;

A4, androstenedione; cfb, change from baseline

In the Applicant's E-R model for serum A4 in pediatric patients, parameter precision of fixed effects appears reasonable based on the 95% CI. Based on the final model predictions, the exposure-response relationship is relatively flat within the studied crinecerfont exposure range.

20.5.6.2.2. GC Percent Change From Baseline

Table 186. Percent Glucocorticoid CFB Final E-R Model (Pediatric)

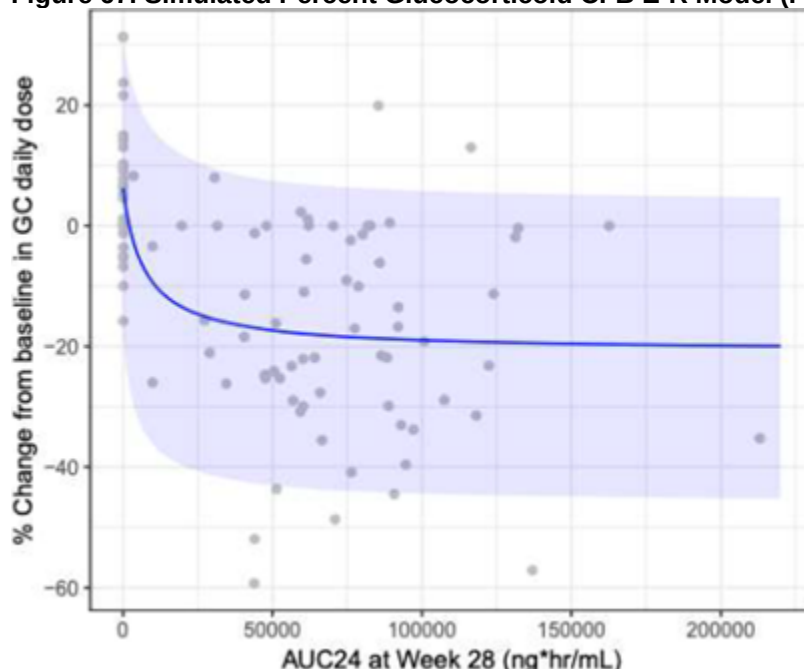
			Estimate	95% CI
Structural model parameters				
INT (%)	θ_1	Intercept	7.03	2.88, 11.2
Emax (%)	θ_2	Maximum effect attributable to the drug	-27.1	-34.2, -19.9
EC50 (ng*hr/mL)	$\exp(\theta_3)$	AUC24 which produces half of Emax	7270	2140, 24800
INT ~ AGE	θ_4	Effect of age on INT	1.08	0.315, 1.85
INT ~ BLGC	θ_5	Effect of baseline GC dose on INT	-1.31	-2.00, -0.626
INT ~ SEX	θ_6	Effect of sex on INT	0.583	-4.99, 6.16
EC50 ~ BLGC	θ_7	Effect of baseline GC dose on EC50	-0.102	-0.272, 0.0684
Residual variance				
Residual	$\Sigma_{(1,1)}$	Additive RUV	196 [SD=14.0]	146, 245

Source: Applicant's E-R report, Table 10.4, page 85

Parameters in the log domain were back-transformed.

Abbreviations: AUC24, area under the plasma concentration-time curve over 24 hours; BLGC, baseline GC; CFB, change from baseline; CI, confidence interval; E-R, exposure-response; GC, glucocorticoid; RUV, residual unexplained variability; SD, standard deviation; SE, standard error

Figure 67. Simulated Percent Glucocorticoid CFB E-R Model (Pediatric), Trial CAH2006



Source: Applicant's E-R report, Figure 13.6, page 103

Grey points represent the observed data; blue line is the model-predicted median; shaded area, 90% CI

Abbreviations: CI, confidence interval; E-R, exposure-response; AUC, area under the concentration-time curve; CFB, change from baseline; GC, glucocorticoid

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In the Applicant's E-R model for % GC reduction at Week 28 from baseline for pediatric patients, the half-maximal effective concentration (EC₅₀) has a relatively wide 95% CI. The effects of sex and baseline GC on intercept also have a relatively wide 95% CI compared to the other covariate effects on the intercept. Null effect is contained within the 95% CI of sex on intercept, indicating minimal impact. Based on the final model predictions, the exposure-response relationship is relatively flat within the studied crinecerfont exposure range.

20.5.6.2.3. GC Daily Dose Reduction to Physiologic Levels at Week 28

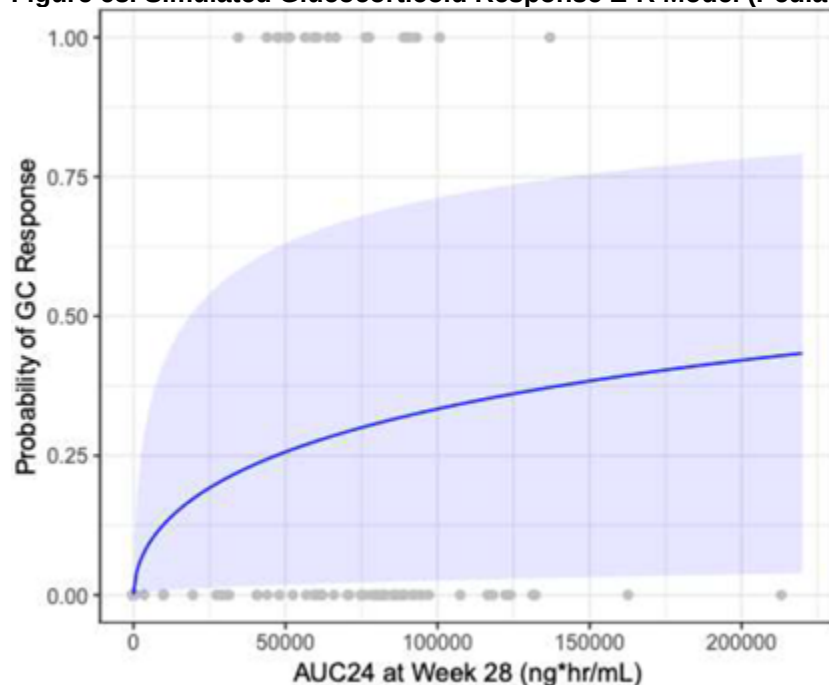
Table 187. Glucocorticoid Response E-R Model (Pediatric)

			Estimate	95% CI
Structural model parameters				
INT	θ_1	Intercept	-7.04	-14.2, -1.39
BETA (ml/(ng*hr))	θ_2	Log-linear slope of drug effect (AUC24)	0.538	-0.0980, 1.17
Covariate effect parameters				
INT ~ AGE	θ_3	Effect of age on INT	-0.198	-0.379, -0.0175
INT ~ BLGC	θ_4	Effect of baseline GC dose on INT	-0.265	-0.497, -0.0337
INT ~ SEX	θ_5	Effect of sex on INT	0.0233	-1.16, 1.20

Source: Applicant's E-R report, Table 10.4, page 85

Abbreviations: AUC24, area under the plasma concentration-time curve over 24 hours; BLGC, baseline GC; CI, confidence interval; E-R, exposure-response; GC, glucocorticoid; RUV, residual unexplained variability; SD, standard deviation; SE, standard error

Figure 68. Simulated Glucocorticoid Response E-R Model (Pediatric), Trial CAH2006

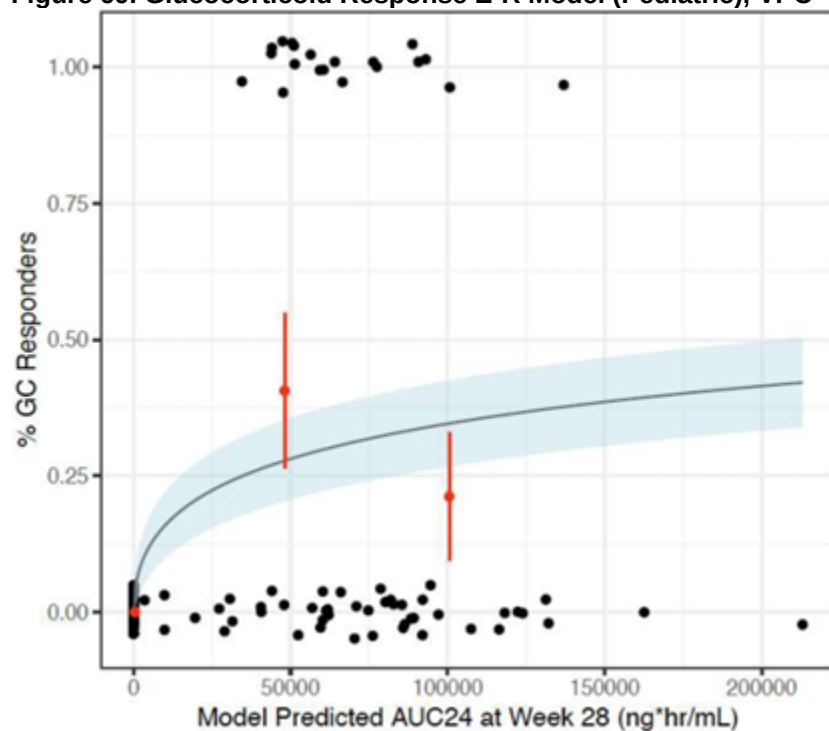


Source: Applicant's E-R report, Figure 13.9, page 109

Grey points represent the observed data; blue line is the model-predicted median; shaded area, 90% CI

Abbreviations: CI, confidence interval; E-R, exposure-response; AUC, area under the concentration-time curve; GC, glucocorticoid

Figure 69. Glucocorticoid Response E-R Model (Pediatric), VPC



Source: Applicant's E-R report, Figure B.53, page 228

Black points represent the observed data; black line represents the model predicted % response overlaid with the 90% CI in blue; the red points represent the mean response for each exposure tertile, with error bars representing 90% CIs

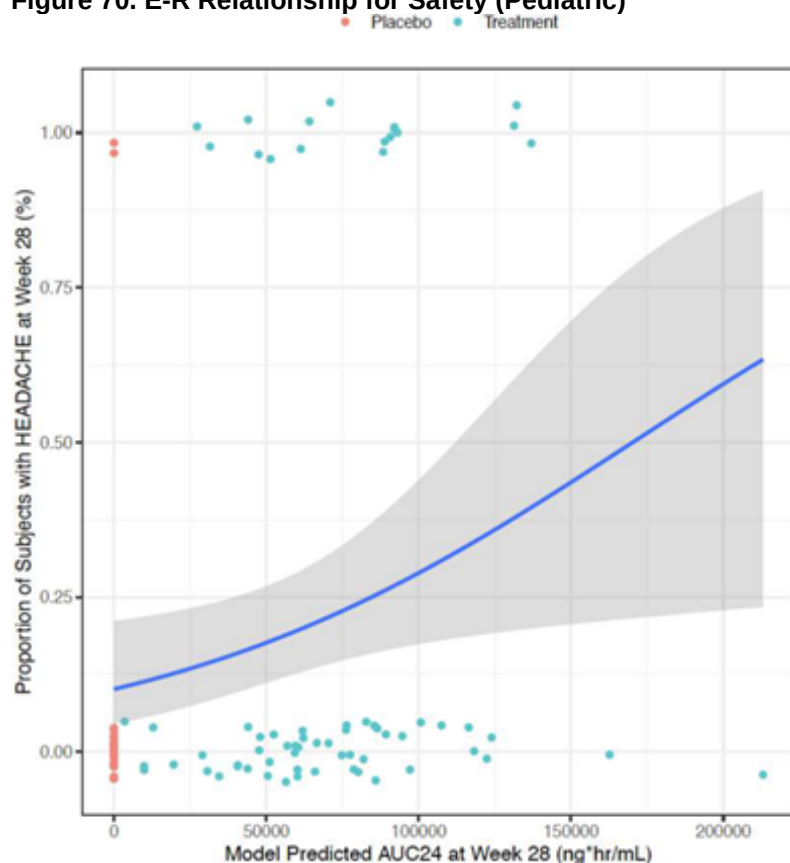
Abbreviations: VPC, visual predictive check; CI, confidence interval; E-R, exposure-response; AUC, area under the concentration-time curve; GC, glucocorticoid

In the Applicant's E-R model for GC response at Week 28 from baseline for pediatric patients, the 95% CIs are relatively wide for all parameter estimates. Null effect is contained within the 95% CI of sex on intercept, indicating minimal impact. Based on the final model predictions, the exposure-response relationship suggests that probability of achieving GC response (i.e., GC dose at physiologic levels) increases as crinecerfont exposure increases (within the range of studied exposure). However, the 95% CI of the slope contains zero, suggesting that other factors may be driving the probability of GC response. Additionally, considering the VPC plot of the observed data and the relatively narrow range of studied exposures reflective of the exposure matching approach, the result suggests that the E-R relationship is relatively flat and maximal response (within the studied exposure) may be achieved in the pediatric patient population.

20.5.6.2.4. Safety

In the pediatric study, TEAEs that occurred with at least 5% greater incidence in the crinecerfont arm compared to placebo were headache (24.6% crinecerfont; 6.1% placebo), upper respiratory tract infection (11.6%, 0%), abdominal pain (7.2%; 0%), fatigue (7.2%; 0%), and streptococcal pharyngitis (5.8%, 0%). Headache had the highest reported frequency in the crinecerfont arm and was, therefore, selected as the AE for exploratory E-R analysis.

Figure 70. E-R Relationship for Safety (Pediatric)



Source: Applicant's E-R report, Figure B.40, page 215

Solid circles represent the data points; the solid blue line represents the LOESS smooth trend line through the data
Abbreviations: E-R, exposure-response; LOESS, locally weighted scatterplot smoothing

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While there is an increasing probability of headache at Week 28 amongst pediatric subjects as crinecerfont exposure increases (within the studied exposure range), the interpretation of this analysis result is limited by the number of subjects who experienced this AE. In total, 17 and 2 subjects had headache in the treatment and placebo arms, respectively. Of note, the incidence of headache in the active arm remains numerically higher than that of the placebo arm (24.6% versus 6.1%, respectively). Overall, the results from the exposure-efficacy and exploratory exposure-safety analyses support the proposed doses for pediatric patients with CAH in achieving clinical benefits and support that no alternative dosing approaches are needed in the pediatric subgroups.

20.6. Pharmacogenetics

Not applicable.

21. Study / Trial Design

21.1. Trial CAH3003

The design of Trial CAH3003 is discussed in Section [12.2.2.1](#). The trial was designed appropriately to meet its stated objectives.

The schedule of assessments for each phase of the trial are shown in [Table 188](#), [Table 189](#) and [Table 190](#).

Table 188. Schedule of Assessments, Trial NBI-74788-CAH3003, Screening and Double-Blind, Placebo-Controlled Treatment Period

Assessment	Screening (Week -4 to Day -1) ^a		Double-Blind, Placebo-Controlled Treatment Period										
	Visit 1	Visit 2 ^b	GC Stable Period ^a		GC Reduction Period ^a						GC Optimization Period ^a		
			Day 1 (Baseline)	Week 2 ^b	Week 4 ^c	Week 6 ^{b,c}	Week 8	Week 9 ^b	Week 10 ^c	Week 12	Week 16 ^b	Week 20 ^b	Week 24
Informed consent	X		X ^d		X ^d								
I/E criteria	X		Update										
Medical history	X		Update										
UDS	X												
Physical exam ^e	X		X		X					X			X
Orthostatics ^f	X		X			X		X		X			X
Vital signs and weight ^g	X		X		X	X		X		X	X	X	X
Chemistry labs	X		X		X	X		X		X	X	X	X
Hematology/coagulation	X		X		X					X			X
Urinalysis	X		X		X					X			X
PK blood sample			X	X	X	X		X		X	X	X	X
CYP21A2 genotyping			X										
Pregnancy test ^h	X (s)		X (u)		X (u)			X (u)		X (u)	X (u)	X (u)	X (u)
Hormone panel ⁱ	X	X	X	X	X	X		X		X	X	X	X
TSH and free T4	X (TSH only)		X		X								X
Urine androgen ^j			X		X								X
Fasting metabolic panel ^k			X										X
Bone markers ^l			X										X
Glucose tolerance test ^m			X										X
Testicular U/S ⁿ			X										X
DXA			X										X
SF-36			X										X
EQ-5D-5L			X										X
MAF			X										X
MOS-12			X										X
PGWBI			X										X
BPRS	X		X							X			X
C-SSRS	X		X		X			X		X	X	X	X
Hirsutism and Acne Scales ^o			X		X					X			X
Menstrual Questionnaire ^o	X		X		X			X		X	X	X	X
12-lead ECG	X		X		X								X
Potential GC reduction					X	X	X		X				

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Screening (Week -4 to Day -1) ^a			Double-Blind, Placebo-Controlled Treatment Period										
			GC Stable Period ^a		GC Reduction Period ^a						GC Optimization Period ^a		
			Day 1 (Baseline)	Week 2 ^b	Week 4 ^c	Week 6 ^{b,c}	Week 8	Week 9 ^b	Week 10 ^c	Week 12	Week 16 ^b	Week 20 ^b	Week 24
Assessment	Visit 1	Visit 2 ^b											
Onsite dosing ^p			X		X							X	
Dispense study drug			X		X				X			X	
Study drug accountability ^q					X				X			X	
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	
Prior and concomitant medications	X		X		X	X	X		X	X	X	X	

Source: Trial NBI-74788-CAH3003 Clinical Protocol Amendment 5.3.1, p. 38-39

a Screening period may be extended by 2 weeks (if needed) for the results of Screening Visit 2 hormone tests. All visits after Day 1 during the glucocorticoid stable period and the glucocorticoid reduction period have a visit window of +5 days; all visits during the glucocorticoid optimization period have a visit window of ±5 days.

b Option of at-home visit or at the study site.

c Within 1 week after Weeks 4, 6, and 10, if a glucocorticoid dose reduction occurred, the study site will call the subject for a safety follow-up. If needed, the subject may come in for an unscheduled visit to perform a safety follow-up (e.g., vital signs, laboratory assessments).

d On Day 1, subjects will review applicable portions of the informed consent form as a reminder about the placebo-controlled design of the study. At Week 4, subjects will review applicable portions of the informed consent form as a reminder that glucocorticoid reduction period has started and about potential symptoms that they may experience.

e Includes measurement of waist circumference.

f After vital signs are obtained, measure blood pressure (single measurement) and heart rate again after the subject has been standing (from a seated position) for approximately 2 minutes. Compare the standing blood pressure versus the average of the three sitting blood pressures for evaluation of orthostasis criteria. Repeat once if abnormal (systolic blood pressure decrease >20 mm Hg, or diastolic blood pressure decrease >10 mm Hg).

g Including height (screening only). Measure blood pressure 3 times, in up to 1-minute intervals, after the subject has been sitting quietly for at least 5 minutes. Height and weight will be measured with subjects not wearing shoes; weight will be measured with subjects not wearing outerwear (e.g., jackets or coats).

h For all females of childbearing potential. Serum pregnancy testing at screening, urine pregnancy tests at other visits.

i Collect blood sample for hormone measurements (adrenocorticotrophic hormone [ACTH], 17-hydroxyprogesterone [17-OHP], cortisol, androstenedione, testosterone, luteinizing hormone [LH], follicle stimulating hormone [FSH], progesterone, plasma renin activity [PRA; measured upright], and sex hormone binding globulin [only for the second blood sample collected at Day 1, Weeks 4 and 24]) in the morning approximately 2 to 3 hours after the morning glucocorticoid dose. At Day 1, Weeks 4 and 24, collect additional blood sample prior to morning glucocorticoid dose. The second blood sample should be collected prior to 1100 hours. Subjects not on a morning glucocorticoid should still have two morning blood samples taken (with the glucose tolerance test and/or before and after the morning study drug dose). The last dose of glucocorticoid taken prior to the first blood sample should be documented.

j Urine sample should be collected by the subject at home starting at midnight the night before the visit until the first morning void after awakening for the day using a container provided to the subject and brought to the study center.

k Collect blood sample after subject fasting at least 8 hours for glucose, insulin, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, and glycated hemoglobin (HbA1c).

l Collect blood sample for osteocalcin, bone-specific alkaline phosphatase, and C-terminal telopeptide (CTX) and collect urine sample (fasting, after first morning void) for N-terminal telopeptide (NTx).

m After an overnight fast (minimum of 8 hours), collect blood samples prior to (within 30 minutes) and approximately 2 hours after 75-gram glucose load (only in subjects without diabetes mellitus).

n For males only.

o For female subjects only. Menstrual questionnaire only for females of childbearing potential not on hormonal or intrauterine device contraceptives.

p Subjects should hold morning study drug dose (except Day 1) and morning glucocorticoid dose (unless not on a morning glucocorticoid). Study drug (except Day 1) and morning glucocorticoid dose (unless not on a morning glucocorticoid) will be taken at study site with breakfast (except Day 1 and Week 24, taken with glucose load). Collect blood samples prior to and approximately 2 hours after dosing at study site.

q Subjects will return all unused study drug, and a compliance check will be performed by counting the capsules returned at each study visit.

Abbreviations: AE, adverse event; BPRS, Brief Psychiatric Rating Scale; C-SSRS, Columbia-Suicide Severity Rating Scale; CYP, cytochrome P450; DXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; ET, early termination; EQ-5D-5L, EuroQol 5-Dimension 5-Level; GC, glucocorticoid; HbA1c, glycated hemoglobin; I/E, inclusion/exclusion; HbAF, Multidimensional Assessment of Fatigue; MOS-12, Medical Outcomes Study 12-item Sleep Scale; PGWBI, Psychological General Well-Being Index; PK, pharmacokinetic; PRA, plasma renin activity; s, serum; SF-36, 36-Item Short Form Health Survey; U/S, ultrasound; T4, thyroxine; TSH, thyroid stimulating hormone; u, urine; UDS, urine drug screen

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Table 189. Schedule of Assessments, Trial NBI-74788-CAH3003, Open-Label and Double-Blind, Active-Controlled Treatment Periods

Assessment	Phone Call	Open-Label Treatment Period ^a					Open-Label or Double-Blind Active-Controlled Treatment Period ^a				Follow-Up Period for Subjects Who Do Not Enter the OLE
		Month 7 ^{b,c}	Month 8 ^c	Month 9 ^{b,c}	Month 10 ^b	Month 12	Month 13 ^{c,d}	Month 14 ^{b,c}	Month 16 ^{b,c}	Month 18/ET ^e	Month 19 ^{a,e}
Physical exam ^f			X			X				X	X
Orthostatics ^g			X	X	X			X ^d	X ^d		
Vital signs and weight ^h		X	X	X	X	X	X	X	X	X	X
Chemistry labs			X	X	X	X		X	X	X	X
Hematology/coagulation		X	X			X	X	X	X	X	X
Urinalysis			X			X				X	X
PK blood sample		X	X	X	X	X	X	X	X	X	X
Pregnancy test ⁱ		X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)	X (u)
Hormone panel ^j		X	X	X	X	X	X	X	X	X	X
TSH and free T4						X				X	
Urine androgen ^k						X	X			X	
Fasting metabolic panel ^l						X				X	
Bone markers ^m						X				X	
Glucose tolerance test ⁿ						X					
Testicular ultrasound ^o						X				X	
DXA ^p						X				X	
SF-36						X				X	
EQ-5D-5L						X				X	
MAF						X				X	
MOS-12						X				X	
PGWBI						X				X	
BPRS						X				X	X
C-SSRS		X	X	X	X	X		X	X	X	X
Hirsutism and Acne Scales ^q			X			X	X			X	X
Menstrual Questionnaire ^q		X	X	X	X	X	X	X	X	X	X
12-lead ECG			X			X	X			X	X
Potential GC reduction		X	X	X			X	X ^d	X ^d		
Onsite dosing ^r						X	X			X	
Dispense study drug			X		X	X		X	X		

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Assessment	Phone Call	Open-Label Treatment Period ^a					Open-Label or Double-Blind Active-Controlled Treatment Period ^a				Follow-Up Period for Subjects Who Do Not Enter the OLE
		Month 7 ^{b,c}	Month 8 ^c	Month 9 ^{b,c}	Month 10 ^b	Month 12	Month 13 ^{c,d}	Month 14 ^{b,c}	Month 16 ^{b,c}	Month 18/ET ^e	Month 19 ^{a,e}
Study drug accountability ^s			X		X	X		X	X	X	
AE monitoring	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant medications		X	X	X	X	X	X	X	X	X	X

Source: Trial NBI-74788-CAH3003 Clinical Protocol Amendment 5.3.1, p. 40-41

a During the open-label or double-blind active-controlled treatment period, visits from Month 7 to Month 10 have a visit window of ± 5 days and visits from Month 12 to Month 18 have a visit window of ± 7 days. The Month 19 (if applicable) visit has a visit window of +7 days.

b At home or study site.

c Within 1 week after the visits at Months 7, 8, 9, 13 (only for rerandomized subjects), 14 (only for rerandomized subjects), and 16 (only for rerandomized subjects), if a glucocorticoid dose reduction occurred, the study site will call the subject for a safety follow-up. If needed, the subject may come in for an unscheduled visit for a safety follow-up (e.g., vital signs, laboratory assessments).

d Only for rerandomized subjects.

e For subjects who discontinue the study prior to Month 18, assessments will be performed at the ET visit and at the follow-up visit (a follow-up visit is not required if the last dose of study drug was at least 28 days prior to the ET visit). Subjects who complete the Month 18 visit and elect to not enter the OLE will undergo a follow-up visit approximately 28 days after last dose of study drug.

f Includes measurement of waist circumference.

g After vital signs are obtained, measure blood pressure (single measurement) and heart rate again after the subject has been standing (from a seated position) for approximately 2 minutes. Compare the standing blood pressure versus the average of the three sitting blood pressures for evaluation of orthostasis criteria. Repeat once if abnormal (systolic blood pressure decrease >20 mm Hg, or diastolic blood pressure decrease >10 mm Hg).

h Measure blood pressure 3 times, in up to 1-minute intervals, after the subject has been sitting quietly for at least 5 minutes. Weight will be measured with subjects not wearing shoes or outerwear (e.g., jackets or coats).

i For all females of childbearing potential.

j Collect blood sample for hormone measurements (adrenocorticotrophic hormone [ACTH], 17-hydroxyprogesterone [17-OHP], cortisol, androstenedione, testosterone, luteinizing hormone [LH], follicle stimulating hormone [FSH], progesterone, plasma renin activity [PRA; measured upright], and sex hormone binding globulin [only for the second blood sample collected at Months 12, 13, and 18]) in the morning approximately 2 to 3 hours after the morning glucocorticoid dose. At Month 12, Month 13 (only for rerandomized subjects), and Month 18/early termination, collect additional blood sample prior to morning glucocorticoid dose. The second blood sample should be collected prior to 1100 hours. Subjects not on a morning glucocorticoid should still have two morning blood samples taken (with the glucose tolerance test and/or before and after the morning study drug dose). The last dose of glucocorticoid taken prior to the first blood sample should be documented.

k Urine sample should be collected by the subject at home starting at midnight the night before the visit until the first morning void after awakening for the day using a container provided to the subject and brought to the study center.

l Collect blood sample after subject fasting at least 8 hours for glucose, insulin, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, and glycated hemoglobin (HbA1c).

m Collect blood sample for osteocalcin, bone-specific alkaline phosphatase, and C-terminal telopeptide (CTx) and collect urine sample (fasting, after first morning void) for N-terminal telopeptide (NTx).

n After an overnight fast (minimum of 8 hours), collect blood samples prior to (within 30 minutes) and approximately 2 hours after 75-gram glucose load (only in subjects without diabetes mellitus).

o For males only. Testicular ultrasound is not required during an early termination visit if the subject had a testicular ultrasound within 3 months prior.

p Not required during an early termination visit if the subject had a DXA within 3 months prior.

q For female subjects only. Menstrual questionnaire only for females of childbearing potential not on hormonal or intrauterine device contraceptives.

r Subjects should hold morning study drug dose and morning glucocorticoid dose (unless not on a morning glucocorticoid). Study drug and morning glucocorticoid dose (unless not on a morning glucocorticoid) will be taken at study site with breakfast (except Month 12, taken with glucose load [only in subjects without diabetes mellitus]). Collect blood samples prior to and approximately 2 hours after dosing at study site.

s Subjects will return all unused study drug, and a compliance check will be performed by counting the capsules returned at each study visit.

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Abbreviations: AE, adverse event; BPRS, Brief Psychiatric Rating Scale; C-SSRS, Columbia-Suicide Severity Rating Scale; DXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; ET, early termination; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FSH, follicle stimulating hormone; GC, glucocorticoid; HbA1c, glycated hemoglobin; I/E, inclusion/exclusion; M12, Month 12; MAF, Multidimensional Assessment of Fatigue; MOS-12, Medical Outcomes Study 12-item Sleep Scale; OLE, open-label extension; PGWBI, Psychological General Well-Being Index; PK, pharmacokinetic; PRA, plasma renin activity; SF-36, 36-Item Short Form Health Survey; T4, thyroxine; TSH, thyroid stimulating hormone; u, urine

Table 190. Schedule of Assessments, Trial NBI-74788-CAH3003, Open-Label Treatment (Month 18 to Month 66) and Follow-Up Periods

Assessment	OLE Treatment Period ^a					OLE Follow-Up Period ^a
	Month 18 ^{b,d}	Month 21 ^{c,d}	Months 24, 36, 48, and 60 ^d	Months 30, 42, 54, and 66 ^d	OLE ET	Final Study Visit Month 67 (Last Dose of Study Drug +4 Weeks)
Informed consent ^b	X					
Physical exam ^e			X	X	X	X
Vital signs and weight ^f		X	X	X	X	X
Chemistry labs		X	X	X	X	X
Hematology/coagulation			X	X	X	X
Urinalysis			X	X	X	X
Pregnancy test ^g		X (u)	X (u)	X (u)	X (u)	X (u)
Hormone panel ^h		X	X	X	X	X
Fasting metabolic panel ⁱ			X			
Glucose tolerance test ^j			X			
Testicular ultrasound ^k			X		X ^k	
DXA			X		X ^l	
SF-36			X		X	
EQ-5D-5L			X		X	
MAF			X		X	
BPRS			X		X	X
C-SSRS		X	X	X	X	X
Hirsutism and Acne Scales ^m			X	X	X	X
Menstrual Questionnaire ^m		X	X	X	X	X
Potential GC or crinecerfont dose adjustment ⁿ	X	X	X	X		
Onsite dosing ^o			X			
Dispense study drug ^p	X	X	X	X		
Study drug accountability ^p		X	X	X	X	
AE monitoring		X	X	X	X	X
Prior and concomitant medications		X	X	X	X	X

Source: Trial NBI-74788-CAH3003 Clinical Protocol Amendment 5.3.1, p. 42-43

a All visits after Month 18 have a visit window of ±14 days, except the Final Study Visit has a visit window of +14 days.

b At Month 18, subjects will review applicable portions of the informed consent form and confirm participation in the optional OLE and should also complete all Month 18 assessments from the Open-Label or Double-Blind Active-Controlled Treatment Period (see Table 2).

c At home or study site.

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d Within 1 week after any glucocorticoid dose reduction, the study site will call the subject for a safety follow-up. If needed, the subject may come in for an unscheduled visit for a safety follow-up (e.g., vital signs, laboratory assessments).

e Includes measurement of waist circumference.

f Measure blood pressure 3 times, in at least 1-minute intervals, after the subject has been sitting quietly for at least 5 minutes. Weight will be measured with subjects not wearing shoes or outerwear (e.g., jackets or coats).

g For all subjects of childbearing potential.

h Collect blood sample for hormone measurements (adrenocorticotrophic hormone [ACTH], 17-hydroxyprogesterone [17-OHP], cortisol, androstenedione, testosterone, luteinizing hormone [LH], follicle stimulating hormone [FSH], progesterone, plasma renin activity [PRA; measured upright], and sex hormone binding globulin [only for the second blood sample collected at Month 24 and every 12 months until Month 60]) in the morning approximately 2 to 3 hours after the morning glucocorticoid dose. At Month 24 and every 12 months until Month 60, collect additional blood sample prior to morning glucocorticoid dose. The second blood sample should be collected prior to 1100 hours. Subjects not on a morning glucocorticoid should still have two morning blood samples taken (with the glucose tolerance test and/or before and after the morning study drug dose). The last dose of glucocorticoid taken prior to the first blood sample should be documented.

i Collect blood sample after subject fasting at least 8 hours for glucose, insulin, total cholesterol, low-density lipoprotein, high-density lipoprotein, triglyceride, and glycated hemoglobin (HbA1c).

j After an overnight fast (minimum of 8 hours), collect blood samples prior to (within 30 minutes) and approximately 2 hours after 75-gram glucose load (only in subjects without diabetes mellitus).

k For subjects with testes only. Testicular ultrasound is not required for an early termination visit if the subject had a testicular ultrasound within 3 months prior.

l DXA is not required for an early termination visit if the subject had a DXA within 3 months prior.

m For female subjects only. Menstrual questionnaire only for subjects of childbearing potential not on hormonal or intrauterine device contraceptives.

n Appendix E, Open-Label Extension Treatment Period Glucocorticoid and Crinecerfont Dose Adjustment Guidance.

o Subjects should hold morning study drug dose (unless not on a morning study drug) and morning glucocorticoid dose (unless not on a morning glucocorticoid). Study drug (unless not on a morning study drug) and morning glucocorticoid dose (unless not on a morning glucocorticoid) will be taken with a glucose load (only in subjects without diabetes mellitus). Collect blood samples prior to and approximately 2 hours after dosing at study site.

p Study drug will be dispensed every 3 months. Subjects will return all unused study drug, and a compliance check will be performed by counting the capsules returned at each study visit.

Abbreviations: AE, adverse event; BPRS, Brief Psychiatric Rating Scale; C-SSRS, Columbia-Suicide Severity Rating Scale; DXA, dual-energy X-ray absorptiometry; ECG, electrocardiogram; ET, early termination; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FSH, follicle stimulating hormone; GC, glucocorticoid; HbA1c, glycated hemoglobin; I/E, inclusion/exclusion; MAF, Multidimensional Assessment of Fatigue; OLE, open-label extension treatment period; PK, pharmacokinetic; PRA, plasma renin activity; SF-36, 36-Item Short Form Health Survey; u, urine

21.2. Trial CAH2006

The design of Trial CAH2006 is discussed in Section [12.2.3.1](#). Schedule of assessments for each phase of the trial are shown in [Table 191](#), [Table 192](#), [Table 193](#), and [Table 194](#). The design was adequate to meet the trial's stated objectives.

Table 191. Schedule of Assessments, Trial NBI-74788-CAH2006, Screening and Double-Blind, Placebo-Controlled and Open-Label Treatment Periods

Assessment	Screening Period ^{a,b}	Double-Blind, Placebo-Controlled Treatment Period ^a							Open-Label Treatment Period ^a					Follow-Up Period for Subjects Not Entering the OLE ^a
	Week -4 to Day -1	Day 1 (Baseline)	Week 4	Week 8 ^b	Week 12 ^{b,c}	Week 16 ^b	Week 20 ^{b,c}	Week 28	Week 32 ^{b,d}	Week 36 ^{b,c}	Week 40 ^b	Week 44 ^{b,c}	Week 52/ET	Week 56 ^e
Informed consent/assent	X													
Inclusion/exclusion criteria	X	Update												
Medical history	X	Update												
TSH and free T4	X (TSH only)	X						X					X	
UDS ^f	X													
Physical exam	X	X						X					X	
Tanner stage ^g	X	X				X		X			X		X	
Vital signs, height, weight ^h	X	X	X			X		X			X		X	X
Hematology/coagulation	X	X	X			X		X	X		X		X	X
Chemistry, cortisol	X	X		X	X	X		X	X	X	X		X	X
Urinalysis	X	X						X					X	X
CYP21A2 genotyping				X										
Pregnancy test ⁱ	X (s)	X (u)	X (u)			X (u)		X (u)			X (u)		X (u)	X (u)
Serial blood sampling (hormone) ^j		X	X											
PK sample(s) incl serial ^k			X			X		X			X		X	
Salivary samples incl serial ^l		X	X	X	X	X	X	X	X	X	X	X	X	
17-OHP, A4, ACTH ^m	X			X	X	X	X	X	X	X	X	X	X	X
Potential GC dose adjustment ^z			X	X	X	X	X		X	X	X	X		
LH, FSH, testosterone, PRA	X	X				X		X			X		X	
Fasting lipids, HOMA-IR ^x		X						X					X	
Bone age ⁿ		X						X					X	
Testicular ultrasound ^o		X						X					X	
EQ-5D ^p		X						X					X	
PedsQL ^q		X						X					X	
PedsQL Family Impact		X						X					X	
BPRS-c ^r	X	X						X					X	

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	Screening Period ^{a,b}	Double-Blind, Placebo-Controlled Treatment Period ^a							Open-Label Treatment Period ^a					Follow-Up Period for Subjects Not Entering the OLE ^a
Assessment	Week -4 to Day -1	Day 1 (Baseline)	Week 4	Week 8 ^b	Week 12 ^{b,c}	Week 16 ^b	Week 20 ^{b,c}	Week 28	Week 32 ^{b,d}	Week 36 ^{b,c}	Week 40 ^b	Week 44 ^{b,c}	Week 52/ET	Week 56 ^e
C-SSRS ^s	X	X	X			X		X			X		X	X
Hirsutism ^t and Acne Scales		X						X					X	
Menstrual Questionnaire ^u	X	X	X			X		X			X		X	X
Palatability/ease of admin ^v			X					X					X	
6- or 12-lead ECG	X	X	X					X					X	X
Dispense study drug		X	X			X		X			X			
Study drug accountability ^w			X			X		X			X		X	
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant meds	X	X	X			X		X			X		X	X

Source: Trial NBI-74788-CAH2006 Clinical Protocol Amendment 3.3, p. 45-47

a The screening period can be extended by up to 4 weeks after discussion with and approval of the medical monitor to allow for delayed screening laboratory results that are needed to determine eligibility or to accommodate other extenuating logistical issues, such as scheduling. The Week 4 visit will have a visit window of ± 5 days, and subsequent visits through Week 52 will have a visit window of ± 7 days. The Week 56 visit (if applicable) visit has a visit window of $+7$ days. All Week 28 assessments should be completed before a subject begins open-label treatment. Not all assessments must be conducted on the same day, but all assessments for a given visit must be completed within the visit window. If a subject's GC regimen is adjusted due to stress dosing, the subject should resume their GC dosing regimen for at least 3 days before their next scheduled lab test if the duration of stress dosing is 3 days or less, and for at least 7 days before their next scheduled lab test if the duration of stress dosing is ≥ 4 days (this 3- or 7-day window supersedes all other visit windows).

b At home or the study site. At Week 16 and Week 40, at home is an option if height is not required. During the screening period, blood and urine collection may be arranged at home.

c Only if a preceding GC dose adjustment occurred.

d Subjects will have further GC adjustment starting at Week 32 only if their Week 32 GC dose is >11 mg/m²/day.

e For subjects who discontinue the study prior to Week 52, assessments will be performed at the ET visit and at the safety follow-up visit, consisting of the same procedures as shown for Week 56 in the schedule of assessments. A safety follow-up visit is not required if the last dose of study drug was at least 4 weeks prior to the ET visit. Subjects who complete the Week 52 visit and elect to not enter the OLE will undergo a safety follow-up visit approximately 4 weeks after last dose of study drug.

f Only for subjects age ≥ 12 years of age.

g Tanner stage at screening and Day 1. Historical assessment of Tanner staging is acceptable if Tanner stage 5 has been previously documented. Tanner staging at subsequent visits is required only if baseline Tanner stage <5 . In addition, subjects with Tanner stage 4 at baseline do not need to undergo Tanner staging at Week 16 or Week 40.

h Measure blood pressure 3 times, in up to 1-minute intervals, after the subject has been sitting quietly for at least 5 minutes. Measure weight with subjects not wearing shoes or outerwear (e.g., jackets or coats). Measure height (in subjects not wearing shoes) as the average of 3 to 6 measurements using a stadiometer (or length board) (Section 9.3.3). Height not required at Week 4 or Week 56 (all subjects) or at Week 16 and Week 40 if growth <2.5 cm in past year, complete fusion of epiphyses on hand/wrist radiograph, or more than 2 years past menarche (females).

i Only for females of childbearing potential. Serum pregnancy testing at screening, urine pregnancy tests at other visits. For subjects with body weight <55 kg, see modified blood sample collection schedules in Appendix B.

j Blood samples for A4, 17-OHP, and ACTH will be collected: For subjects with body weight <55 kg, see modified blood sample collection schedules for subjects with a body weight <55 kg in Appendix B. For subjects who are ≥ 6 years of age with a body weight ≥ 55 kg: On Day 1 and Week 4 approximately 15 minutes before and just prior to dosing with the morning GC and (Week 4) study drug between approximately 0800 and 0830 hours and at 2, 3, 4, and 6 hours after dosing. Any midday GC dose the subject is receiving should be taken after blood is sampled 6 hours after dosing. All subjects should take their glucocorticoid dose the night before prior to 2100 hours.

k For all subjects, a blood sample for PK prior to the morning study dose will be collected at Weeks 4, 16, 28, 40, and 52/ET, if ET occurs prior to Week 52. At Week 4: for subjects who are ≥ 6 years of age with a body weight ≥ 35 kg, blood samples for PK will also be collected approximately 2, 3, 4, and 6 hours after dosing.

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l Salivary samples for adrenal androgens and precursors will be collected:

–Day 1 and Weeks 4, 28, and 52/ET: at approximately 0600 hours, at approximately 0800 hours prior to dosing with morning GC and (after Day 1) study drug and at approximately 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of GC; if subject is not on an evening GC dose, then prior to bedtime. Any midday GC dose that the subject is receiving should be taken after the salivary sample collection 6 hours after dosing.

–Weeks 8, 12, 16, 20, 32, 36, 40, and 44: prior to morning GC dose at approximately the same time as the blood sample. If a blood sample is not obtained at a visit (e.g., because no GC dose adjustment was required), a salivary sample does not need to be obtained.

m For subjects with body weight <55 kg, see modified blood sample collection schedules in Appendix B. Subjects should take their GC dose the night before prior to 2100 hours and hold their morning dose of GC, fludrocortisone (if applicable), and study drug (except screening) until after predose blood sample collection. The blood sample collection will include 17-OHP and A4 at all visits, and will also include ACTH at Weeks 16, 28, 40, 52/ET, and 56. Morning dosing should occur between approximately 0800 and 0830 hours with breakfast. At Week 28 and Week 52/ET, another blood sample will be collected at 3 hours after dosing for subjects ≥6 years of age with body weight ≥20 kg.

n Only in females with the most recent prior bone age <14 years and males with the most recent prior bone age <16 years. Bone age assessment is not required at the ET visit if the subject had a bone age assessment within 3 months prior.

o Only in male subjects. Week 28 and Week 52/ET ultrasound only if testicular adrenal rest tumor(s) demonstrated on Day 1. Testicular ultrasound is not required at the ET visit if the subject had a testicular ultrasound within 3 months prior.

p EQ-5D-Y for age 8 to 15 years, EQ-5D-5L for age 16 years and older.

q PedsQL Toddler Version for age 2 to 4 years, Young Child Version for age 5 to 7 years, Child Version for age 8 to 12 years, Adolescent Version for age 13 to 17 years.

r Only for subjects ≥3 years of age.

s Only for subjects ≥6 years of age. Baseline/Screening version used at screening, and Since Last Visit version at subsequent visits.

t Hirsutism scale only for females.

u Menstrual Cycle Questionnaire only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives.

v Palatability will be assessed for subjects ≥6 years of age, and ease of administration will be assessed by caregivers of subjects <6 years of age. The palatability/ease of administration assessment should be administered within approximately 15 minutes after study drug dosing.

w Subjects will return all unused study drug and packaging, and a compliance check will be performed.

x For subjects with body weight <55 kg, see modified blood sample collection in Appendix B.

z Glucocorticoid dose adjustment should be considered based on hormone results, expected to be available within 7 to 14 days of blood sample collection.

Abbreviations: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotrophic hormone; admin, administration; AE, adverse event; BPRS-c, Brief Psychiatric Rating Scale, Children's Version; C-SSRS, Columbia-Suicide Severity Rating Scale; CYP, cytochrome P450; ECG, electrocardiogram; ET, early termination; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FSH, follicle-stimulating hormone; GC, glucocorticoid; HOMA-IR, homeostatic model assessment of insulin resistance; incl, including; LH, luteinizing hormone; OLE, open-label extension; PedsQL, Pediatric Quality of Life Instrument; PK, pharmacokinetic; PRA, plasma renin activity; s, serum; T4, thyroxine; TSH, thyroid-stimulating hormone; u, urine; UDS, urine drug screen

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Table 192. Schedule of Assessments, Trial NBI-74788-CAH2006, Open-Label Extension (Month 12 [Week 52] Onward)

Assessment	Month 12 (Week 52) ^{b,c}	OLE ^a					OLE ET	OLE Follow-Up Period ^a
		Month 13 (Only if Evening Crinecerfont Dose Doubled the Previous Month)	Month 18 and Every 12 Months Thereafter ^c	Month 19 (Only if Evening Crinecerfont Dose Doubled the Previous Month)	Month 24 and Every 12 Months Thereafter ^c	Month 25 and Every 6 Months Thereafter (Only if Evening Crinecerfont Dose Doubled the Previous Month)		Final Study Visit (~4 Weeks After Last Dose of Study Drug) ^d
Informed consent/assent ^e	X							
Physical exam		X		X	X	X	X	
TSH and free T4					X			
Tanner stage ^f			X		X		X	
Vital signs, height, weight ^g		X	X	X	X	X	X	X
6- or 12-lead ECG		X		X		X	X	
Hematology/coagulation			X		X		X	X
Chemistry, cortisol		X	X	X	X	X	X	X
Urinalysis					X		X	X
Urine pregnancy test ^h					X		X	X
PK sample(s) ⁱ		X	X ^j	X	X ^j	X		
Salivary samples incl serial ^k					X		X	
17-OHP, A4, ACTH		X	X	X	X ^l	X	X	X
LH, FSH, testosterone, PRA		X	X	X	X	X	X	
Fasting lipids, HOMA-IR			X		X		X	
Bone age ^m			X		X		X	
Testicular ultrasound ⁿ	X ⁿ				X		X	
EQ-5D ^o					X		X	
BPRS-c ^p					X		X	
C-SSRS ^q			X		X		X	X
Hirsutism ^r and Acne Scales			X		X		X	
Menstrual Questionnaire ^s			X		X		X	X
Dispense study drug ^t	X		X		X			
Study drug accountability ^u			X		X		X	
AE monitoring		X	X	X	X	X	X	X
Prior and concomitant medications		X	X	X	X	X	X	X

Source: Trial NBI-74788-CAH2006 Clinical Protocol Amendment 3.3, p. 48-49

a The Month 12 (Week 52) will have a visit window of ±7 days. Each 6-month visit (Month 12, 24, 30, 36, etc.) will have a visit window of ±14 days. The visit 4 weeks following doubling of the evening dose will have a visit window of ±7 days relative to the visit at which the dose was increased; and the final study visit will have a visit window of +14 days.

b The Month 12 (Week 52) visit in the OLE is the same as the Week 52/ET visit in the open-label treatment period. Please refer to Table 7 for the Week 52 assessments.

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c Within 2 weeks after any GC dose reduction, the investigator will contact the subject's parent(s)/guardians for a safety follow-up. If needed, the subject may come in for an unscheduled visit for a safety follow-up (e.g., vital signs, laboratory assessments).

d This visit is not required if the last dose of study drug was at least 4 weeks prior to the early termination visit, or if the subject transitions during the OLE to commercially available crinecerfont or to another crinecerfont study.

e At the Month 12 (Week 52) visit, the subject's parent(s) or legal guardian(s) (or the subject if the subject has reached the age of majority) will review applicable portions of the ICF and the subject will review applicable portions of the assent form (if applicable) to confirm the subject's participation in the optional OLE. Subjects should also complete all Month 12 (Week 52) assessments from the open-label treatment period (see Table 7).

f Subjects who have been assessed as Tanner stage 5 at any visit are not required to undergo assessment of Tanner stage at subsequent visits.

g Measure blood pressure 3 times, in up to 1-minute intervals, after the subject has been sitting quietly for at least 5 minutes. Measure weight with subjects not wearing shoes or outerwear (e.g., jackets or coats). Measure height (in subjects not wearing shoes) as the average of 3 to 6 measurements using a stadiometer (or length board) (Section 9.7.3). Height should be assessed at each 6-month visit.

h Only for females of childbearing potential.

i For all subjects, a blood sample for PK prior to the morning study dose will be collected at Week 52 visit as part of the open-label treatment period (see Table 7).

j Only for subjects who had their evening dose of crinecerfont doubled at the previous 6-month visit. Further PK samples will not be required during the OLE after the PK samples obtained 1 month and 6 months following a dose increase for inadequate efficacy.

k For all subjects at Month 24 and every 12 months, and at ET visit, salivary samples for adrenal androgens and precursors will be collected at approximately 0600 hours, at approximately 0800 hours prior to dosing with morning GC and study drug, approximately 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of GC; if subject is not on an evening GC dose, then prior to bedtime. Salivary samples at approximately 0800 hours prior to and 3 and 6 hours after the morning GC dose should occur at approximately the same time as the corresponding blood samples (as applicable). Any midday GC dose that the subject is receiving should be taken after the 6-hour postdose blood and salivary samples are collected.

l At these visits, subjects should take their GC dose the night before prior to 2100 hours and hold their morning dose of GC, fludrocortisone (if applicable), and study drug until after predose blood sample collection. Dosing with the morning GC, fludrocortisone (if applicable), and study drug should occur between approximately 0800 and 0830 hours with breakfast. At Month 24 and every 12 months thereafter, and at ET, another blood sample will be collected at 3 hours after dosing for subjects ≥ 6 years of age with body weight ≥ 20 kg. For subjects weighing ≥ 20 and < 35 kg only, a single ACTH sample will be collected prior to the morning glucocorticoid dose.

m Only in females with the most recent prior bone age < 14 years and males with the most recent prior bone age < 16 years. Bone age assessment is not required at the early termination visit if the subject had a bone age assessment within 3 months prior.

n All male subjects continuing in the OLE will have a testicular ultrasound at Week 52, including subjects who are not required to have a Week 52 ultrasound as part of the core study. An ultrasound will be performed at Month 24 and every 12 months thereafter only if the Week 52 ultrasound demonstrates the presence of TARTs. All male subjects will have a testicular ultrasound at the early termination visit except for subjects who have had a testicular ultrasound within 3 months prior to the early termination visit.

o EQ-5D-Y for age 8 to 15 years, EQ-5D-5L for age ≥ 16 years. Subjects entering the OLE will have age recalculated and use the appropriate EQ-5D instrument based on age of entry into the OLE.

p Only for subjects ≥ 3 years of age. In the OLE, the BPRS-c will continue to be administered to subjects who are ≥ 18 years of age.

q Only for subjects ≥ 6 years of age.

r Hirsutism scale only for females.

s Menstrual Cycle Questionnaire only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives.

t Study drug will be dispensed every 3 months.

u Subjects will return all unused study drug, and a compliance check will be performed by counting the capsules returned, at each study visit except for the additional visits that occur 1 month after doubling of the evening dose for inadequate efficacy.

Abbreviations: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; AE, adverse event; BPRS-c, Brief Psychiatric Rating Scale for Children; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; ET, early termination; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FSH, follicle-stimulating hormone; GC, glucocorticoid; HOMA-IR, homeostatic model assessment of insulin resistance; ICF, informed consent form; LH, luteinizing hormone; OLE, open-label extension; PK, pharmacokinetic; PRA, plasma renin activity; T4, thyroxine; TART, testicular adrenal rest tumor; TSH, thyroid-stimulating hormone

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Table 193. Schedule of Assessments, Trial NBI-74788-CAH2006, Double-Blind, Placebo-Controlled and Open-Label Treatment Periods

Assessment	Screening Period ^{a,b}	Double-Blind, Placebo-Controlled Treatment Period ^a							Open-Label Treatment Period ^a					Follow-Up Period for Subjects Not Entering the OLE ^a
	Week -4 to Day -1	Day 1 (Baseline)	Week 4	Week 8 ^b	Week 12 ^{b,c}	Week 16 ^b	Week 20 ^{b,c}	Week 28	Week 32 ^{b,d}	Week 36 ^{b,c}	Week 40 ^b	Week 44 ^{b,c}	Week 52/ET	Week 56 ^e
Informed consent/assent	X													
Inclusion/exclusion criteria	X	Update												
Medical history	X	Update												
TSH and free T4	X (TSH only)	X						X					X	
UDS ^f	X													
Physical exam	X	X						X					X	
Tanner stage ^g	X	X				X		X			X		X	
Vital signs, height, weight ^h	X	X	X			X		X			X		X	X
Hematology/coagulation	X	X	X			X		X	X		X		X	X
Chemistry, cortisol	X	X		X	X	X		X	X	X	X		X	X
Urinalysis	X	X						X					X	X
CYP21A2 genotyping				X										
Pregnancy test ⁱ	X (s)	X (u)	X (u)			X (u)		X (u)			X (u)		X (u)	X (u)
Serial blood sampling (hormone) ^j		X	X											
PK sample(s) incl serial ^k			X			X		X			X		X	
Salivary samples incl serial ^l		X	X	X	X	X	X	X	X	X	X	X	X	
17-OHP, A4, ACTH ^m	X			X	X	X	X	X	X	X	X	X	X	X
Potential GC dose adjustment ^z			X	X	X	X	X		X	X	X	X		
LH, FSH, testosterone, PRA	X	X				X		X			X		X	
Fasting lipids, HOMA-IR ^x		X						X					X	
Bone age ⁿ		X						X					X	
Testicular ultrasound ^o		X						X					X	
EQ-5D ^p		X						X					X	
PedsQL ^q		X						X					X	
PedsQL Family Impact		X						X					X	
BPRS-c ^r	X	X						X					X	
C-SSRS ^s	X	X	X			X		X			X		X	X
Hirsutism ^t and Acne Scales		X						X					X	
Menstrual Questionnaire ^u	X	X	X			X		X			X		X	X

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Assessment	Screening Period ^{a,b}	Double-Blind, Placebo-Controlled Treatment Period ^a							Open-Label Treatment Period ^a					Follow-Up Period for Subjects Not Entering the OLE ^a
	Week -4 to Day -1	Day 1 (Baseline)	Week 4	Week 8 ^b	Week 12 ^{b,c}	Week 16 ^b	Week 20 ^{b,c}	Week 28	Week 32 ^{b,d}	Week 36 ^{b,c}	Week 40 ^b	Week 44 ^{b,c}	Week 52/ET	Week 56 ^e
Palatability/ease of admin ^v			X					X					X	
6- or 12-lead ECG	X	X	X					X					X	X
Dispense study drug		X	X			X		X			X			
Study drug accountability ^w			X			X		X			X		X	
AE monitoring	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Prior and concomitant meds	X	X	X			X		X			X		X	X

Source: Trial NBI-74788-CAH2006 Clinical Protocol Amendment 3.3, p. 45-47

a The screening period can be extended by up to 4 weeks after discussion with and approval of the medical monitor to allow for delayed screening laboratory results that are needed to determine eligibility or to accommodate other extenuating logistical issues, such as scheduling. The Week 4 visit will have a visit window of ±5 days, and subsequent visits through Week 52 will have a visit window of ±7 days. The Week 56 visit (if applicable) visit has a visit window of +7 days. All Week 28 assessments should be completed before a subject begins open-label treatment. Not all assessments must be conducted on the same day, but all assessments for a given visit must be completed within the visit window. If a subject's GC regimen is adjusted due to stress dosing, the subject should resume their GC dosing regimen for at least 3 days before their next scheduled lab test if the duration of stress dosing is 3 days or less, and for at least 7 days before their next scheduled lab test if the duration of stress dosing is ≥4 days (this 3- or 7-day window supersedes all other visit windows).

b At home or the study site. At Week 16 and Week 40, at home is an option if height is not required. During the screening period, blood and urine collection may be arranged at home.

c Only if a preceding GC dose adjustment occurred.

d Subjects will have further GC adjustment starting at Week 32 only if their Week 32 GC dose is >11 mg/m²/day.

e For subjects who discontinue the study prior to Week 52, assessments will be performed at the ET visit and at the safety follow-up visit, consisting of the same procedures as shown for Week 56 in the schedule of assessments. A safety follow-up visit is not required if the last dose of study drug was at least 4 weeks prior to the ET visit. Subjects who complete the Week 52 visit and elect to not enter the OLE will undergo a safety follow-up visit approximately 4 weeks after last dose of study drug.

f Only for subjects age ≥12 years of age.

g Tanner stage at screening and Day 1. Historical assessment of Tanner staging is acceptable if Tanner stage 5 has been previously documented. Tanner staging at subsequent visits is required only if baseline Tanner stage <5. In addition, subjects with Tanner stage 4 at baseline do not need to undergo Tanner staging at Week 16 or Week 40.

h Measure blood pressure 3 times, in up to 1-minute intervals, after the subject has been sitting quietly for at least 5 minutes. Measure weight with subjects not wearing shoes or outerwear (e.g., jackets or coats). Measure height (in subjects not wearing shoes) as the average of three to six measurements using a stadiometer (or length board) (Section 9.3.3). Height not required at Week 4 or Week 56 (all subjects) or at Week 16 and Week 40 if growth <2.5 cm in past year, complete fusion of epiphyses on hand/wrist radiograph, or more than 2 years past menarche (females).

i Only for females of childbearing potential. Serum pregnancy testing at screening, urine pregnancy tests at other visits. For subjects with body weight <55 kg, see modified blood sample collection schedules in Appendix B.

j Blood samples for A4, 17-OHP, and ACTH will be collected: For subjects with body weight <55 kg, see modified blood sample collection schedules for subjects with a body weight <55 kg in Appendix B. For subjects who are ≥6 years of age with a body weight ≥55 kg: On Day 1 and Week 4 approximately 15 minutes before and just prior to dosing with the morning GC and (Week 4) study drug between approximately 0800 and 0830 hours and at 2, 3, 4, and 6 hours after dosing. Any midday GC dose the subject is receiving should be taken after blood is sampled 6 hours after dosing. All subjects should take their glucocorticoid dose the night before prior to 2100 hours.

k For all subjects, a blood sample for PK prior to the morning study dose will be collected at Weeks 4, 16, 28, 40, and 52/ET, if ET occurs prior to Week 52. At Week 4: for subjects who are ≥6 years of age with a body weight ≥35 kg, blood samples for PK will also be collected approximately 2, 3, 4, and 6 hours after dosing.

l Salivary samples for adrenal androgens and precursors will be collected:

–Day 1 and Weeks 4, 28, and 52/ET: at approximately 0600 hours, at approximately 0800 hours prior to dosing with morning GC and (after Day 1) study drug and at approximately 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of GC; if subject is not on an evening GC dose, then prior to bedtime. Any midday GC dose that the subject is receiving should be taken after the salivary sample collection 6 hours after dosing.

–Weeks 8, 12, 16, 20, 32, 36, 40, and 44: prior to morning GC dose at approximately the same time as the blood sample. If a blood sample is not obtained at a visit (e.g., because no GC dose adjustment was required), a salivary sample does not need to be obtained.

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m For subjects with body weight <55 kg, see modified blood sample collection schedules in Appendix B. Subjects should take their GC dose the night before prior to 2100 hours and hold their morning dose of GC, fludrocortisone (if applicable), and study drug (except screening) until after predose blood sample collection. The blood sample collection will include 17-OHP and A4 at all visits, and will also include ACTH at Weeks 16, 28, 40, 52/ET, and 56. Morning dosing should occur between approximately 0800 and 0830 hours with breakfast. At Week 28 and Week 52/ET, another blood sample will be collected at 3 hours after dosing for subjects ≥6 years of age with body weight ≥20 kg.

n Only in females with the most recent prior bone age <14 years and males with the most recent prior bone age <16 years. Bone age assessment is not required at the ET visit if the subject had a bone age assessment within 3 months prior.

o Only in male subjects. Week 28 and Week 52/ET ultrasound only if testicular adrenal rest tumor(s) demonstrated on Day 1. Testicular ultrasound is not required at the ET visit if the subject had a testicular ultrasound within 3 months prior.

p EQ-5D-Y for age 8 to 15 years, EQ-5D-5L for age 16 years and older.

q PedsQL Toddler Version for age 2 to 4 years, Young Child Version for age 5 to 7 years, Child Version for age 8 to 12 years, Adolescent Version for age 13 to 17 years.

r Only for subjects ≥3 years of age.

s Only for subjects ≥6 years of age. Baseline/Screening version used at screening, and Since Last Visit version at subsequent visits.

t Hirsutism scale only for females.

u Menstrual Cycle Questionnaire only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives.

v Palatability will be assessed for subjects ≥6 years of age, and ease of administration will be assessed by caregivers of subjects <6 years of age. The palatability/ease of administration assessment should be administered within approximately 15 minutes after study drug dosing.

w Subjects will return all unused study drug and packaging, and a compliance check will be performed.

x For subjects with body weight <55 kg, see modified blood sample collection in Appendix B.

z Glucocorticoid dose adjustment should be considered based on hormone results, expected to be available within 7 to 14 days of blood sample collection.

Abbreviations: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; admin, administration; AE, adverse event; BPRS-c, Brief Psychiatric Rating Scale, Children's Version; C-SSRS, Columbia-Suicide Severity Rating Scale; CYP, cytochrome P450; ECG, electrocardiogram; ET, early termination; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FSH, follicle-stimulating hormone; GC, glucocorticoid; HOMA-IR, homeostatic model assessment of insulin resistance; incl, including; LH, luteinizing hormone; OLE, open-label extension; PedsQL, Pediatric Quality of Life Instrument; PK, pharmacokinetic; PRA, plasma renin activity; s, serum; T4, thyroxine; TSH, thyroid-stimulating hormone; u, urine; UDS, urine drug screen

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Table 194. Schedule of Assessments, Trial NBI-74788-CAH2006, Open-Label Extension (Week 52 Onward)

Assessment	OLE ^a						OLE ET	OLE Follow-Up Period ^a
	Month 12 (Week 52) ^{b,c}	Month 13 (Only if Evening Crinecerfont Dose Doubled the Previous Month)	Month 18 and Every 12 Months Thereafter ^c	Month 19 (Only if Evening Crinecerfont Dose Doubled the Previous Month)	Month 24 and Every 12 Months Thereafter ^c	Month 25 and Every 6 Months Thereafter (Only if Evening Crinecerfont Dose Doubled the Previous Month)		
Informed consent/assent ^e	X							
Physical exam		X		X	X	X	X	
TSH and free T4					X			
Tanner stage ^f			X		X		X	
Vital signs, height, weight ^g		X	X	X	X	X	X	X
6- or 12-lead ECG		X		X		X	X	
Hematology/coagulation			X		X		X	X
Chemistry, cortisol		X	X	X	X	X	X	X
Urinalysis					X		X	X
Urine pregnancy test ^h					X		X	X
PK sample(s) ⁱ		X	X ^j	X	X ^j	X		
Salivary samples incl serial ^k					X		X	
17-OHP, A4, ACTH		X	X	X	X ^l	X	X	X
LH, FSH, testosterone, PRA		X	X	X	X	X	X	
Fasting lipids, HOMA-IR			X		X		X	
Bone age ^m			X		X		X	
Testicular ultrasound ⁿ	X ⁿ				X		X	
EQ-5D ^o					X		X	
BPRS-c ^p					X		X	
C-SSRS ^q			X		X		X	X
Hirsutism ^r and Acne Scales			X		X		X	
Menstrual Questionnaire ^s			X		X		X	X
Dispense study drug ^t	X		X		X			
Study drug accountability ^u			X		X		X	
AE monitoring		X	X	X	X	X	X	X
Prior and concomitant medications		X	X	X	X	X	X	X

Source: Trial NBI-74788-CAH2006 Clinical Protocol Amendment 3.3, p. 48-49

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- a The Month 12 (Week 52) will have a visit window of ± 7 days. Each 6-month visit (Month 12, 24, 30, 36, etc.) will have a visit window of ± 14 days. The visit 4 weeks following doubling of the evening dose will have a visit window of ± 7 days relative to the visit at which the dose was increased; and the final study visit will have a visit window of $+14$ days.
- b The Month 12 (Week 52) visit in the OLE is the same as the Week 52/ET visit in the open-label treatment period. Please refer to Table 7 for the Week 52 assessments.
- c Within 2 weeks after any GC dose reduction, the investigator will contact the subject's parent(s)/guardians for a safety follow-up. If needed, the subject may come in for an unscheduled visit for a safety follow-up (e.g., vital signs, laboratory assessments).
- d This visit is not required if the last dose of study drug was at least 4 weeks prior to the early termination visit, or if the subject transitions during the OLE to commercially available crinecerfont or to another crinecerfont study.
- e At the Month 12 (Week 52) visit, the subject's parent(s) or legal guardian(s) (or the subject if the subject has reached the age of majority) will review applicable portions of the ICF and the subject will review applicable portions of the assent form (if applicable) to confirm the subject's participation in the optional OLE. Subjects should also complete all Month 12 (Week 52) assessments from the open-label treatment period (see Table 7).
- f Subjects who have been assessed as Tanner stage 5 at any visit are not required to undergo assessment of Tanner stage at subsequent visits.
- g Measure blood pressure 3 times, in up to 1-minute intervals, after the subject has been sitting quietly for at least 5 minutes. Measure weight with subjects not wearing shoes or outerwear (e.g., jackets or coats). Measure height (in subjects not wearing shoes) as the average of 3 to 6 measurements using a stadiometer (or length board) (Section 9.7.3). Height should be assessed at each 6-month visit.
- h Only for females of childbearing potential.
- i For all subjects, a blood sample for PK prior to the morning study dose will be collected at Week 52 visit as part of the open-label treatment period (see Table 7).
- j Only for subjects who had their evening dose of crinecerfont doubled at the previous 6-month visit. Further PK samples will not be required during the OLE after the PK samples obtained 1 month and 6 months following a dose increase for inadequate efficacy.
- k For all subjects at Month 24 and every 12 months, and at ET visit, salivary samples for adrenal androgens and precursors will be collected at approximately 0600 hours, at approximately 0800 hours prior to dosing with morning GC and study drug, approximately 3 and 6 hours after dosing, and within 30 minutes prior to the evening dose of GC; if subject is not on an evening GC dose, then prior to bedtime. Salivary samples at approximately 0800 hours prior to and 3 and 6 hours after the morning GC dose should occur at approximately the same time as the corresponding blood samples (as applicable). Any midday GC dose that the subject is receiving should be taken after the 6-hour postdose blood and salivary samples are collected.
- l At these visits, subjects should take their GC dose the night before prior to 2100 hours and hold their morning dose of GC, fludrocortisone (if applicable), and study drug until after predose blood sample collection. Dosing with the morning GC, fludrocortisone (if applicable), and study drug should occur between approximately 0800 and 0830 hours with breakfast. At Month 24 and every 12 months thereafter, and at ET, another blood sample will be collected at 3 hours after dosing for subjects ≥ 6 years of age with body weight ≥ 20 kg. For subjects weighing ≥ 20 and < 35 kg only, a single ACTH sample will be collected prior to the morning glucocorticoid dose.
- m Only in females with the most recent prior bone age < 14 years and males with the most recent prior bone age < 16 years. Bone age assessment is not required at the early termination visit if the subject had a bone age assessment within 3 months prior.
- n All male subjects continuing in the OLE will have a testicular ultrasound at Week 52, including subjects who are not required to have a Week 52 ultrasound as part of the core study. An ultrasound will be performed at Month 24 and every 12 months thereafter only if the Week 52 ultrasound demonstrates the presence of TARTs. All male subjects will have a testicular ultrasound at the early termination visit except for subjects who have had a testicular ultrasound within 3 months prior to the early termination visit.
- o EQ-5D-Y for age 8 to 15 years, EQ-5D-5L for age ≥ 16 years. Subjects entering the OLE will have age recalculated and use the appropriate EQ-5D instrument based on age of entry into the OLE.
- p Only for subjects ≥ 3 years of age. In the OLE, the BPRS-c will continue to be administered to subjects who are ≥ 18 years of age.
- q Only for subjects ≥ 6 years of age.
- r Hirsutism scale only for females.
- s Menstrual Cycle Questionnaire only for females who have undergone menarche and are not on hormonal or intrauterine device contraceptives.
- t Study drug will be dispensed every 3 months.
- u Subjects will return all unused study drug, and a compliance check will be performed by counting the capsules returned, at each study visit except for the additional visits that occur 1 month after doubling of the evening dose for inadequate efficacy.
- Abbreviations: 17-OHP, 17-hydroxyprogesterone; A4, androstenedione; ACTH, adrenocorticotropic hormone; AE, adverse event; BPRS-c, Brief Psychiatric Rating Scale for Children; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; ET, early termination; EQ-5D-5L, EuroQol 5-Dimension 5-Level; FSH, follicle-stimulating hormone; GC, glucocorticoid; HOMA-IR, homeostatic model assessment of insulin resistance; ICF, informed consent form; LH, luteinizing hormone; OLE, open-label extension; PK, pharmacokinetic; PRA, plasma renin activity; T4, thyroxine; TART, testicular adrenal rest tumor; TSH, thyroid-stimulating hormone

21.3. Columbia-Suicide Severity Rating Scale

The Columbia Suicide Severity Rating Scale was used to screen for suicidal ideation and behavior during trials CAH3003 and CAH2006. The questionnaire content is shown in [Figure 71](#).

Figure 71. Columbia-Suicide Severity Rating Scale Questions

Always ask questions 1 and 2.		Past Month
1) Have you wished you were dead or wished you could go to sleep and not wake up?		
2) Have you actually had any thoughts about killing yourself?		
If YES to 2, ask questions 3, 4, 5 and 6. If NO to 2, skip to question 6.		
3) Have you been thinking about how you might do this?		
4) Have you had these thoughts and had some intention of acting on them?		High Risk
5) Have you started to work out or worked out the details of how to kill yourself? Did you intend to carry out this plan?		High Risk
Always Ask Question 6	Life-time	Past 3 Months
6) Have you done anything, started to do anything, or prepared to do anything to end your life? Examples: Took pills, tried to shoot yourself, cut yourself, tried to hang yourself, or collected pills, obtained a gun, gave away valuables, wrote a will or suicide note, took out pills but didn't swallow any, held a gun but changed your mind or it was grabbed from your hand, went to the roof but didn't jump, etc. If yes, was this within the past 3 months?		High Risk

Source: <https://cssrs.columbia.edu/the-columbia-scale-c-ssrs/about-the-scale/> Accessed: 26 October 2024.

Scoring Scale

- 0 – No suicidal ideation
- 1 – Wish to be dead
- 2 – Nonspecific active suicidal thoughts
- 3 – Active suicidal ideation with methods without intent to act
- 4 – Active suicidal ideation with some intent to act, without specific plan
- 5 – Active suicidal ideation with specific plan and intent

22. Efficacy

The efficacy assessment was based on the two phase 3 trials, CAH3003 in adults and CAH2006 in children. The efficacy findings are discussed in [Section 12.2](#) of this document.

The two phase 2 dose-finding trials—Trial CAH2001 in adults with CAH and Trial CAH2008 in pediatric subjects with CAH—informed dosing for the phase 3 trials and are discussed in [Section 12.1](#) of this document.

The review team conducted additional subgroup analyses of the primary efficacy endpoint for trials CAH3003 in adults and CAH2006 in children.

Subgroup Analysis of Primary Endpoint

Trial CAH3003

Analyses of the primary endpoint by subgroup showed that the glucocorticoid total daily dose decreased from baseline to Week 24 in the crinecerfont group, compared with the placebo group, in all prespecified subgroups ([Figure 72](#)). Interpretation of 95% CIs in some subgroups was limited by their small sample sizes and likely some random highs and random lows in sample estimates of subgroup treatment effects. Therefore, we also derived shrinkage estimates of subgroup treatment effects using a Bayesian hierarchical model based on summary sample estimates.

The total variability in the sample estimates is the sum of the within-subgroup variability of the sample estimator and the across-subgroups variability in underlying/true parameter values. Shrinkage estimates of the subgroup treatment effect, which borrows information from the other subgroups while estimating the treatment effect for a specific subgroup, is a “weighted” average of the sample estimate and overall estimate. The weights are based on the ratio of the between-subgroup variability to the within-subgroup variability. The greater that ratio, the smaller the weight on the overall estimate (the less the shrinkage).

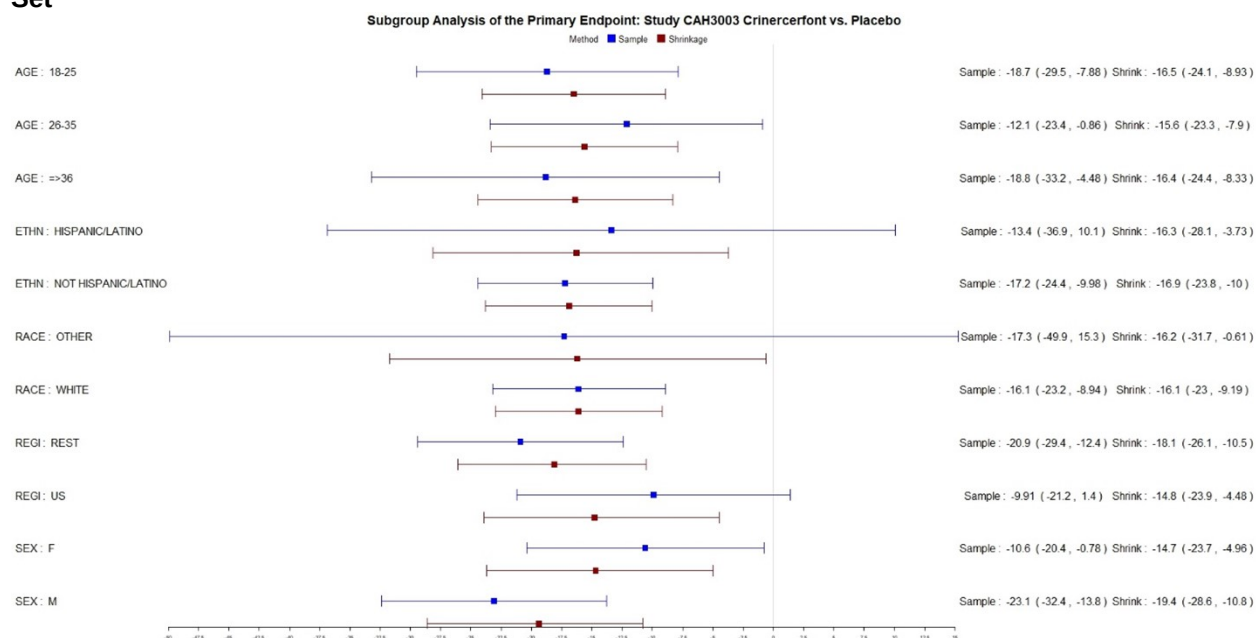
For $i = 1, 2, \dots, n$; Y_i represents the observed sample estimate of treatment effect in a subgroup level i , assume $Y_i \sim N(\mu_i, \sigma_i^2)$ where:

- σ_i^2 are the observed variance for sample estimates,
- $\mu_i \sim N(\mu, \tau^2)$, and
- $\mu \sim N(0, 400)$, $1/\tau^2 \sim \text{Gamma}(0.001, 0.001)$.

The variance of 400 for the hyper-prior $\mu \sim N(0, \text{variance} = 400)$, was chosen as $4 \times \text{Residual Variance}$ of the treatment effect.

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Figure 72. Forest Plot of LS Mean Differences of Percent Change From Baseline at Week 24 in Glucocorticoid Total Daily Dose in Different Subgroups, Trial NBI-74788-CAH3003, Full Analysis Set



Source: Statistical reviewer's analysis

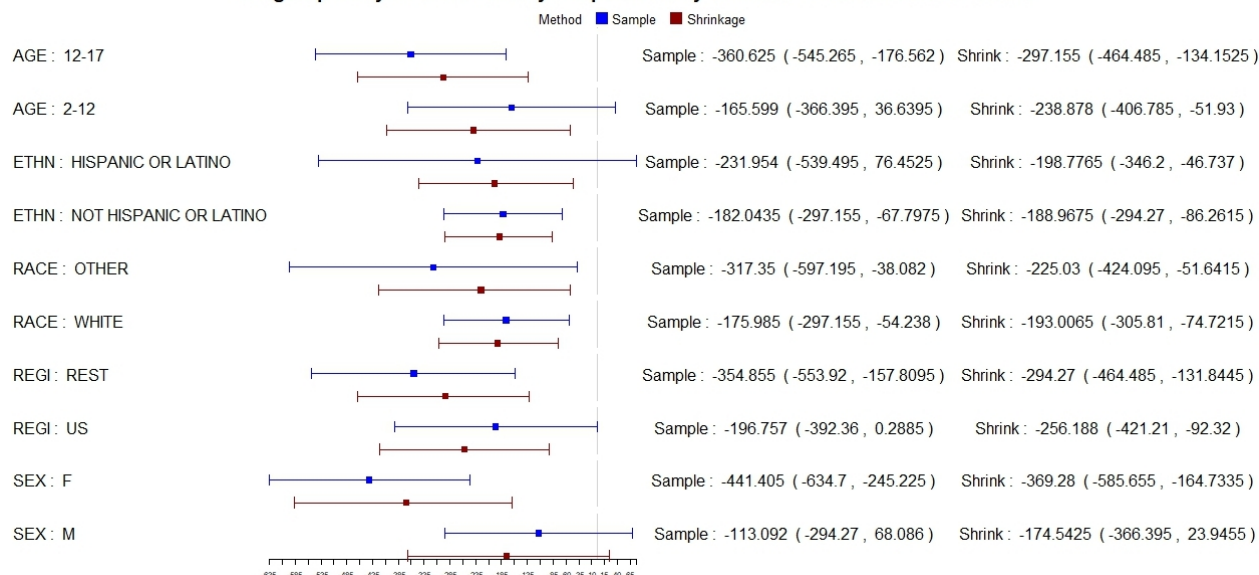
Subjects not meeting the androstenedione control criteria, had their glucocorticoid daily dose percent change from baseline values set to 0 at each visit where control was not met. Due to small number of participants Black or African American, American Indian or Alaska Native and Asian were combined into OTHER category of Race.

Abbreviations: ETHN, ethnicity; F, female; LS, least squares; M, male; REGI, region; REST, rest of world; US, United States

Trial CAH2006

Similar to Trial CAH3003, subgroup analyses of the primary endpoint showed that serum androstenedione (ng/dL) decreased from baseline to Week 4 in the crinecerfont group, compared with the placebo group, in all prespecified subgroups ([Figure 73](#)).

Figure 73. Forest Plot of LS Mean Differences of Change From Baseline at Week 4 in Serum Androstenedione (ng/dL) in Different Subgroups, Trial NBI-74788-CAH2006, Full Analysis Set
Subgroup Analysis of the Primary Endpoint: Study CAH2006 Crinecerfont vs. Placebo



Source: Statistical reviewer's analysis

Interpretation of 95% CIs in some subgroups such as Hispanic/Latino subgroups, 2 to <12 years of age etc. was limited by their small sample sizes (N<20). Due to small number of participants Black or African American, American Indian or Alaska Native and Asian were combined into OTHER category of Race.

Abbreviations: CI, confidence interval; ETHN, ethnicity; LS, least squares; F, female; M, male; REGI, region; REST, rest of world; US, United States

Subgroup analyses for both the trials showed consistent treatment effects across multiple important subgroups.

23. Clinical Safety

23.1. Abuse Potential

The FDA controlled substance staff (CSS) reviewed the drug abuse liability assessment of crinecerfont. In a memorandum to NDA 218808 and finalized in Document Archiving, Reporting, and Regulatory Tracking System (DARRTS) on October 23, 2024, CSS concluded:

- The receptor binding and activity data indicate that crinecerfont is a CRF1 receptor antagonist. Receptor binding studies demonstrated that crinecerfont did not bind to any receptors, transporters, or ion channels typically associated with drugs having a potential for abuse.
- Additional studies including nonclinical abuse potential assessments and a human abuse potential study were not requested.
- A review of TEAEs in clinical studies did not reveal any evidence to suggest that crinecerfont has a potential for abuse or physical dependence. The most prevalent AEs observed in clinical trials were fatigue, headache, and pyrexia.

- The proposed drug product, if approved under this NDA, will not require a Drug Abuse and Dependence section in its label.

CSS concluded that crinecerfont does not appear to have abuse potential and should not be controlled under the Controlled Substances Act. Crinecerfont does not require a Section 9 (Drug Abuse and Dependence section) in its label.

23.2. Laboratory Analyses, Trial CAH3003

23.2.1. Chemistry, Trial CAH3003

There were no meaningful differences between crinecerfont and placebo groups in mean change from baseline in any chemistry parameter during the double-blind treatment period. Renal function remained stable (see [Figure 74](#) and [Figure 75](#)) and lipid parameters in both treatment groups declined slightly during the double-blind treatment phase ([Figure 76](#)).

Outlier analysis tables for chemistry and renal function parameters are shown in [Table 195](#) and [Table 196](#). Other than what was discussed in earlier sections of this review, there were no clinically meaningful differences in incidences of laboratory parameters outside the normal range between treatment groups. The higher incidence of low bicarbonate (<20 mEq/L) and low calcium (<8.4 mg/dL) with crinecerfont vs. placebo in this trial was not observed in the pediatric trial; this lack of consistency across trials reduces the likelihood that these findings are drug-related.

Outlier analysis for lipid parameters is shown in [Table 197](#). The greater frequency of outliers in some of the lipid parameters in the crinecerfont group is not clinically meaningful because the mean change from baseline was not significant and not significantly different from placebo (figures included).

Table 195. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=122 n/N _w (%)	Placebo N=59 n/N _w (%)	Risk Difference % (95% CI)
Sodium, low (mEq/L)			
Level 1 (<132)	12/121 (9.9)	7/59 (11.9)	-1.9 (-13.5, 7.1)
Level 2 (<130)	3/121 (2.5)	5/59 (8.5)	-6.0 (-16.1, 0.4)
Level 3 (<125)	1/121 (0.8)	2/59 (3.4)	-2.6 (-10.8, 1.7)
Sodium, high (mEq/L)			
Level 1 (>150)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 2 (>155)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 3 (>160)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Potassium, low (mEq/L)			
Level 1 (<3.6)	7/121 (5.8)	6/59 (10.2)	-4.4 (-15.2, 3.5)
Level 2 (<3.4)	4/121 (3.3)	0/59 (0)	3.3 (-2.9, 8.2)
Level 3 (<3)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)

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CRENESSITY (crinecerfont) oral capsule and oral solution

Laboratory Parameter	Crinecerfont N=122 n/N_w (%)	Placebo N=59 n/N_w (%)	Risk Difference % (95% CI)
Potassium, high (mEq/L)			
Level 1 (>5.5)	2/121 (1.7)	2/59 (3.4)	-1.7 (-10.1, 3.1)
Level 2 (>6)	1/121 (0.8)	1/59 (1.7)	-0.9 (-8.3, 3.1)
Level 3 (>6.5)	0/121 (0)	1/59 (1.7)	-1.7 (-9.0, 1.4)
Chloride, low (mEq/L)			
Level 1 (<95)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 2 (<88)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 3 (<80)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Chloride, high (mEq/L)			
Level 1 (>108)	14/121 (11.6)	5/59 (8.5)	3.1 (-7.8, 11.8)
Level 2 (>112)	1/121 (0.8)	0/59 (0)	0.8 (-5.3, 4.6)
Level 3 (>115)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Bicarbonate, low (mEq/L)			
Level 1 (<20)	13/121 (10.7)	2/59 (3.4)	7.4 (-1.7, 14.8)
Level 2 (<18)	4/121 (3.3)	1/59 (1.7)	1.6 (-5.9, 6.8)
Level 3 (<15)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Bicarbonate, high (mEq/L)			
Level 3 (>30)	18/121 (14.9)	9/59 (15.3)	-0.4 (-12.9, 10.0)
Glucose, low (mg/dL)			
Level 1 (<70)	17/121 (14.0)	10/59 (16.9)	-2.9 (-15.6, 7.7)
Level 2 (<54)	1/121 (0.8)	2/59 (3.4)	-2.6 (-10.8, 1.7)
Level 3 (<40)	1/121 (0.8)	1/59 (1.7)	-0.9 (-8.3, 3.1)
Glucose, fasting, high (mg/dL)			
Level 1 (≥100 to 125)	8/118 (6.8)	5/57 (8.8)	-2.0 (-12.8, 5.9)
Level 2 (≥126)	0/118 (0)	1/57 (1.8)	-1.8 (-9.3, 1.5)
Glucose, random, high (mg/dL)			
Level 2 (≥200)	0/121 (0)	1/59 (1.7)	-1.7 (-9.0, 1.4)
Level 3 (>250)	0/121 (0)	1/59 (1.7)	-1.7 (-9.0, 1.4)
Calcium, low (mg/dL)			
Level 1 (<8.4)	5/121 (4.1)	1/59 (1.7)	2.4 (-5.2, 8.0)
Level 2 (<8)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 3 (<7.5)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Calcium, high (mg/dL)			
Level 1 (>10.5)	1/121 (0.8)	1/59 (1.7)	-0.9 (-8.3, 3.1)
Level 2 (>11)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 3 (>12)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Magnesium, low (mg/dL)			
Level 1 (<1.5)	2/121 (1.7)	0/59 (0)	1.7 (-4.5, 5.8)
Level 2 (<1.2)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 3 (<0.9)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Magnesium, high (mg/dL)			
Level 1 (>2.3)	9/121 (7.4)	6/59 (10.2)	-2.7 (-13.7, 5.5)
Level 2 (>4)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 3 (>7)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Phosphate, low (mg/dL)			
Level 1 (<2.5)	8/121 (6.6)	5/59 (8.5)	-1.9 (-12.4, 5.8)
Level 2 (<2)	1/121 (0.8)	0/59 (0)	0.8 (-5.3, 4.6)
Level 3 (<1.4)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Protein, total, low (g/dL)			
Level 1 (<6)	1/121 (0.8)	1/59 (1.7)	-0.9 (-8.3, 3.1)
Level 2 (<5.4)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 3 (<5)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)

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Laboratory Parameter	Crinecerfont N=122 n/N _w (%)	Placebo N=59 n/N _w (%)	Risk Difference % (95% CI)
Albumin, low (g/dL)			
Level 1 (<3.1)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 2 (<2.5)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 3 (<2)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
CPK, high (U/L)			
Level 1 (>3× ULN)	11/121 (9.1)	7/59 (11.9)	-2.8 (-14.3, 6.1)
Level 2 (>5× ULN)	8/121 (6.6)	0/59 (0)	6.6 (0.3, 12.5)*
Level 3 (>10× ULN)	5/121 (4.1)	0/59 (0)	4.1 (-2.1, 9.3)
Blood urea nitrogen, high (mg/dL)			
Level 1 (>23)	8/121 (6.6)	5/59 (8.5)	-1.9 (-12.4, 5.8)
Level 2 (>27)	2/121 (1.7)	2/59 (3.4)	-1.7 (-10.1, 3.1)
Level 3 (>31)	1/121 (0.8)	0/59 (0)	0.8 (-5.3, 4.6)

Source: adlb.xpt; Software: R

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Table 196. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=122 n/N _w (%)	Placebo N=59 n/N _w (%)	Risk Difference % (95% CI)
Creatinine, high (mg/dL)			
Level 1 (≥1.5× baseline)	1/121 (0.8)	2/59 (3.4)	-2.6 (-10.8, 1.7)
Level 2 (≥2× baseline)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
Level 3 (≥3× baseline)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)
eGFR, low (mL/min/1.73 m ²)			
Level 1 (≥25% decrease)	4/114 (3.5)	4/56 (7.1)	-3.6 (-13.8, 3.1)
Level 2 (≥50% decrease)	0/114 (0)	0/56 (0)	0.0 (-6.5, 3.3)
Level 3 (≥75% decrease)	0/114 (0)	0/56 (0)	0.0 (-6.5, 3.3)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

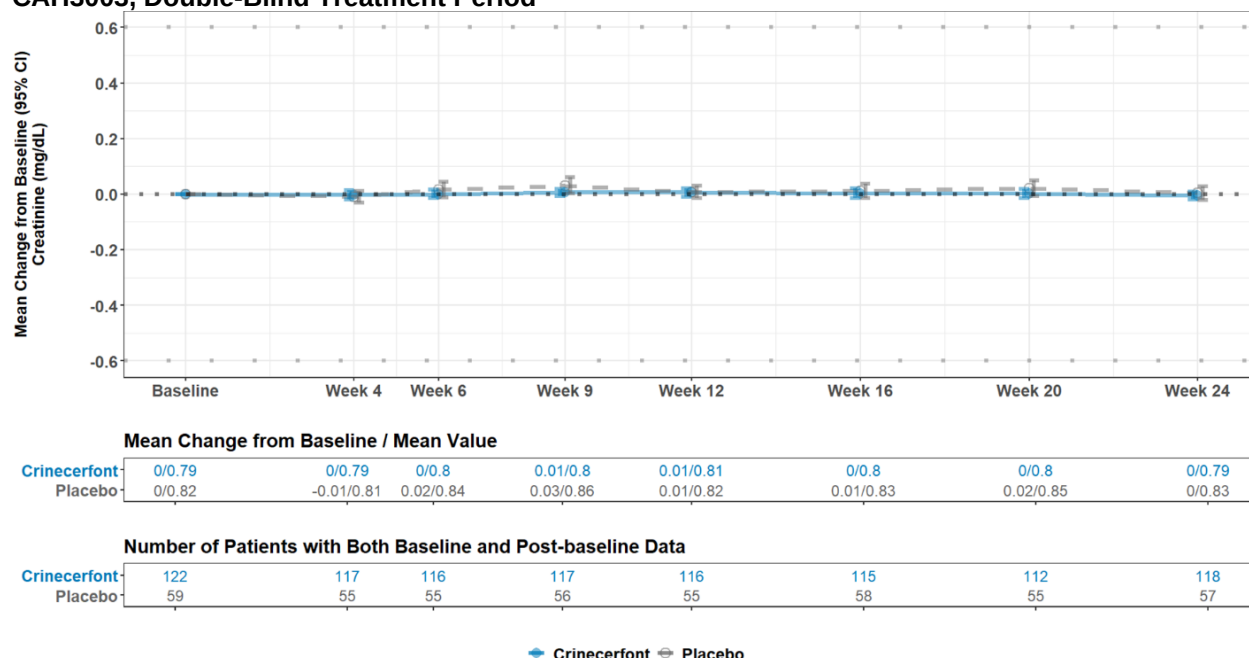
In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

eGFR values are calculated from serum creatinine using chronic kidney disease epidemiology collaboration (CKD-EPI) equation.

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

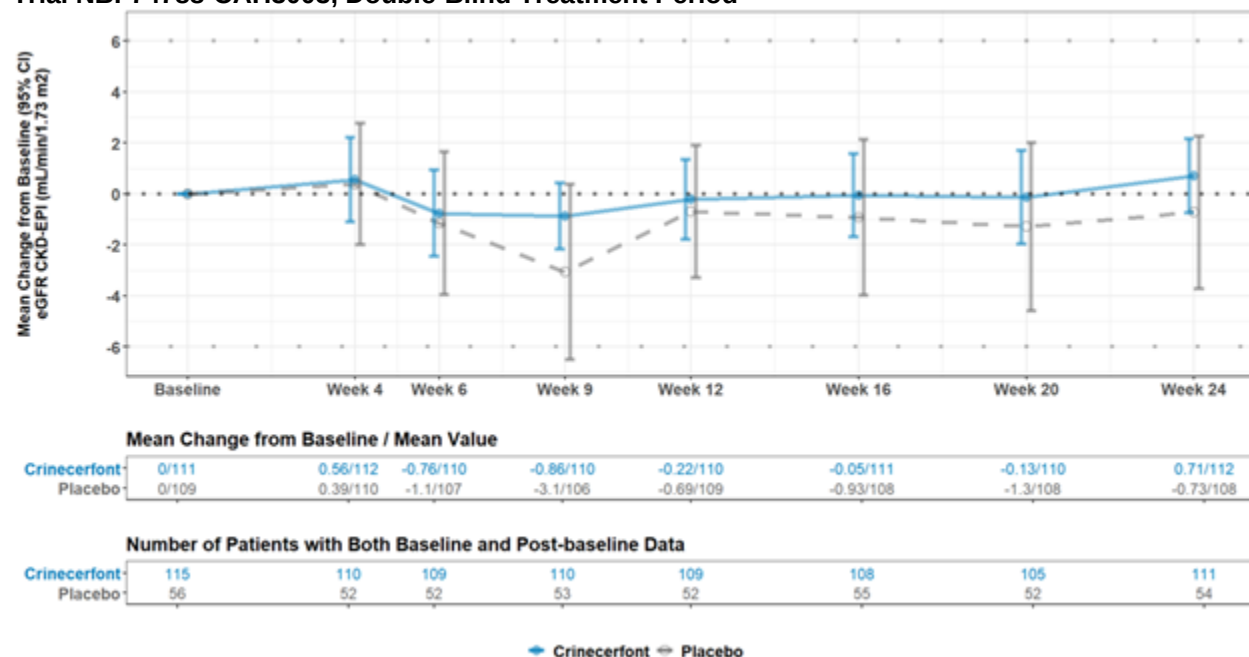
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CRENESSITY (crinecerfont) oral capsule and oral solution

Figure 74. Mean Creatinine Change From Baseline Over Time, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



Source: adlb.xpt; Software: R
Abbreviations: CI, confidence interval

Figure 75. Change From Baseline in Mean eGFR (ml/min/1.73 m²) Over Time, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



Source: adlb.xpt; Software: R
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.
eGFR values are calculated from serum creatinine using the CKD-EPI equation.
Abbreviations: CI, confidence interval; CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; eGFR, estimated glomerular filtration rate

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

Table 197. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=122 n/N_w (%)	Placebo N=59 n/N_w (%)	Risk Difference % (95% CI)
Cholesterol, total, high (mg/dL)			
Level 1 (>200)	30/118 (25.4)	9/58 (15.5)	9.9 (-3.5, 21.4)
Level 2 (>210)	18/118 (15.3)	8/58 (13.8)	1.5 (-11.0, 11.8)
Level 3 (>225)	10/118 (8.5)	5/58 (8.6)	-0.1 (-10.9, 8.1)
HDL, males, low (mg/dL)			
Level 1 (<40)	18/59 (30.5)	7/30 (23.3)	7.2 (-13.5, 25.0)
Level 2 (<30)	3/59 (5.1)	0/30 (0)	5.1 (-6.6, 14.0)
Level 3 (<20)	0/59 (0)	0/30 (0)	0.0 (-11.5, 6.2)
HDL, females, low (mg/dL)			
Level 1 (<50)	26/59 (44.1)	14/28 (50.0)	-5.9 (-27.6, 16.0)
Level 2 (<40)	7/59 (11.9)	4/28 (14.3)	-2.4 (-21.0, 11.6)
Level 3 (<20)	0/59 (0)	0/28 (0)	0.0 (-12.2, 6.2)
LDL, high (mg/dL)			
Level 1 (>130)	25/118 (21.2)	8/58 (13.8)	7.4 (-5.5, 18.3)
Level 2 (>160)	7/118 (5.9)	3/58 (5.2)	0.8 (-8.7, 7.7)
Level 3 (>190)	2/118 (1.7)	0/58 (0)	1.7 (-4.6, 6.0)
Triglycerides, high (mg/dL)			
Level 1 (>150)	17/118 (14.4)	7/58 (12.1)	2.3 (-9.7, 12.2)
Level 2 (>300)	1/118 (0.8)	1/58 (1.7)	-0.9 (-8.4, 3.2)
Level 3 (>500)	0/118 (0)	0/58 (0)	0.0 (-6.2, 3.2)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 24 weeks.

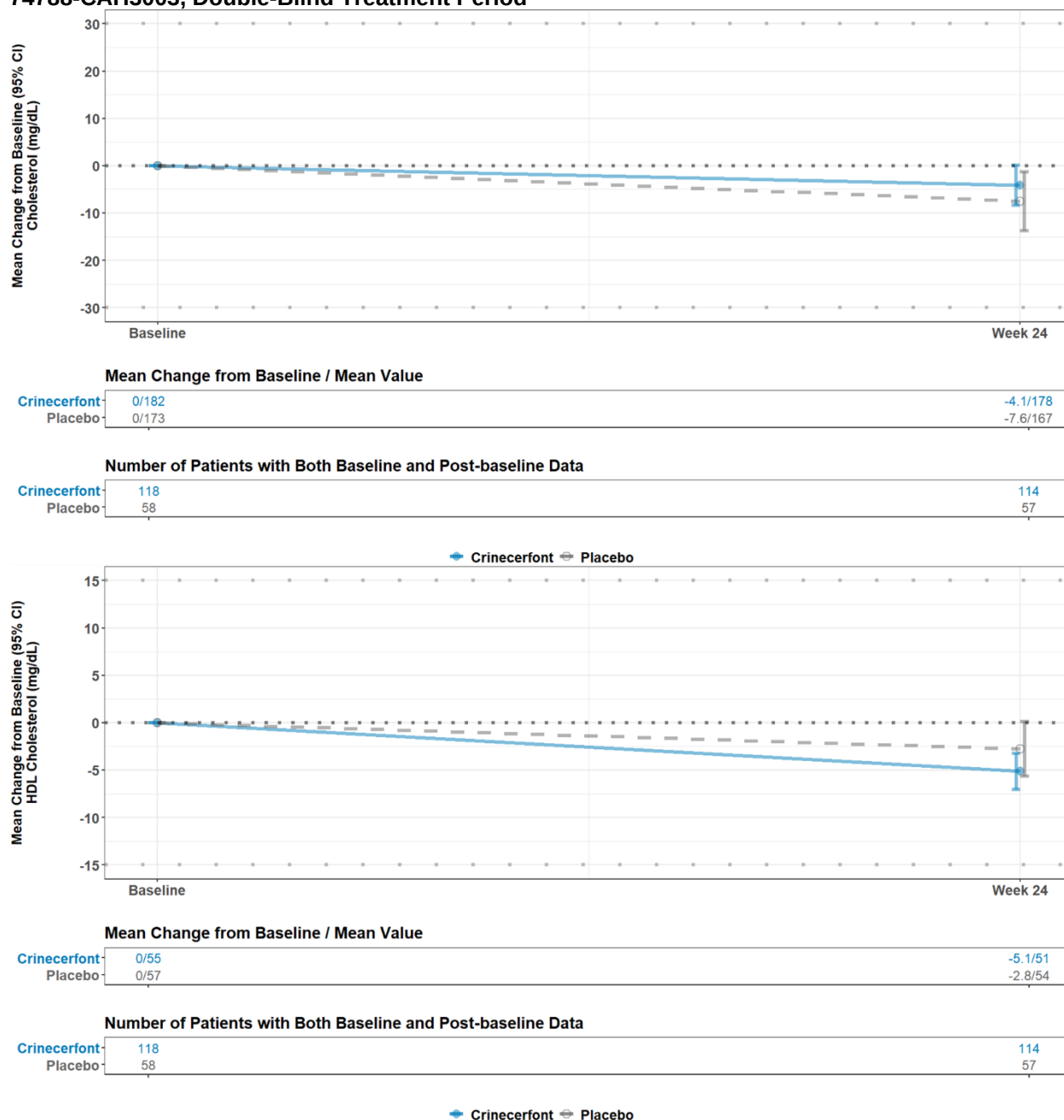
Risk difference (with 95% confidence interval) is shown between treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

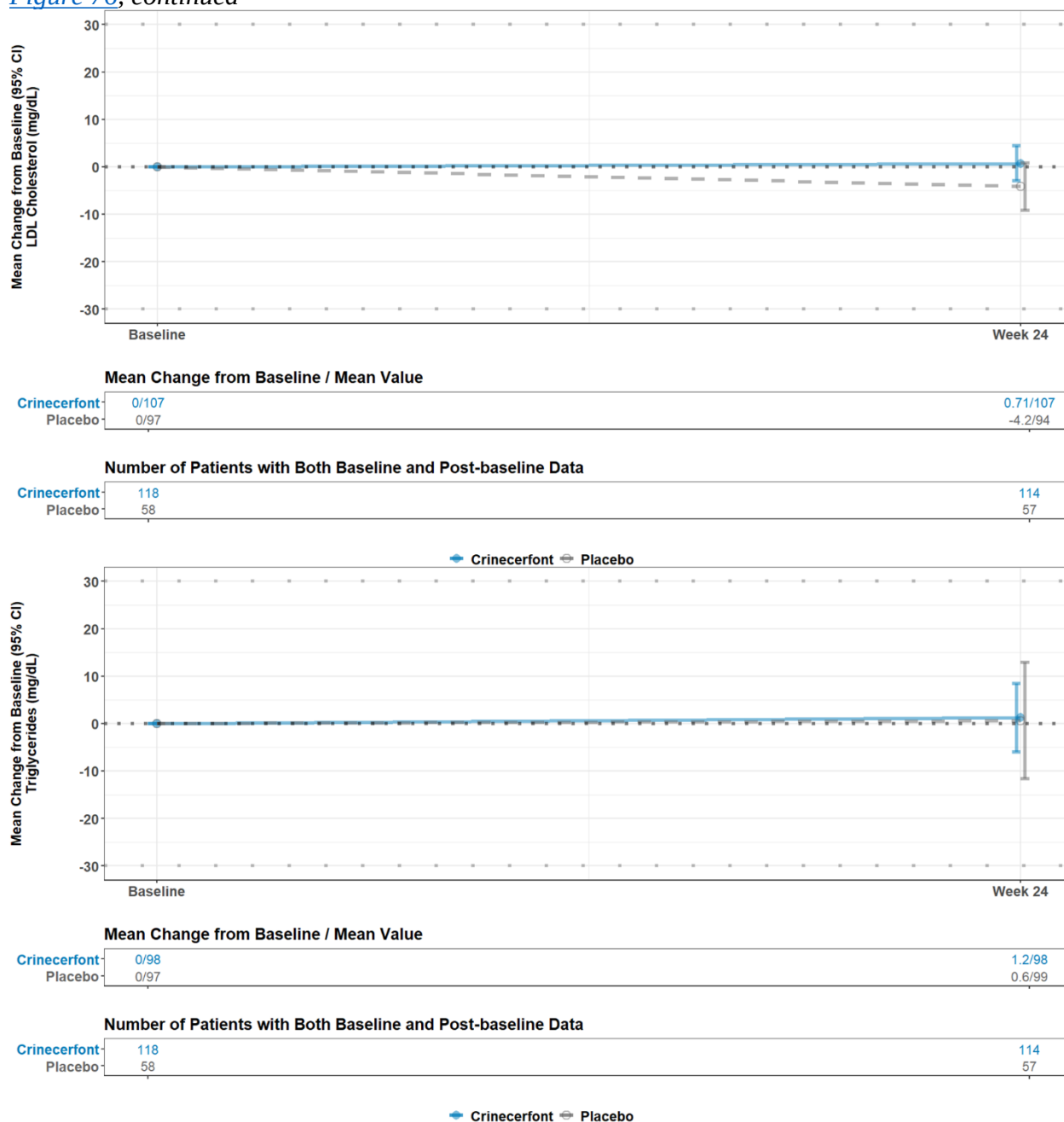
NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

Figure 76. Mean Lipid Parameter Change From Baseline Over Time, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



Continued

Figure 76, continued



Source: adlb.xpt; Software: R
Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein

23.2.2. Hematology, Trial CAH3003

Other than what was discussed in earlier sections of this review regarding neutrophil and white blood cell counts, there were no clinically meaningful differences in incidence of hematology parameters outside the normal range between treatment groups ([Table 198](#)).

Table 198. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=122 n/N_w (%)	Placebo N=59 n/N_w (%)	Risk Difference % (95% CI)
<i>Complete Blood Count</i>			
WBC, low (10 ³ cells/μL)			
Level 1 (<3.5)	2/121 (1.7)	2/58 (3.4)	-1.8 (-10.2, 3.0)
Level 2 (<3)	0/121 (0)	0/58 (0)	0.0 (-6.2, 3.1)
Level 3 (<1)	0/121 (0)	0/58 (0)	0.0 (-6.2, 3.1)
WBC, high (10 ³ cells/μL)			
Level 1 (>10.8)	12/121 (9.9)	13/58 (22.4)	-12.5 (-25.6, -1.5)*
Level 2 (>13)	2/121 (1.7)	5/58 (8.6)	-7.0 (-17.2, -0.9)*
Level 3 (>15)	0/121 (0)	3/58 (5.2)	-5.2 (-14.2, -1.8)*
Hemoglobin, low (g/dL)			
Level 2 (>1.5 g/dL dec. from baseline)	3/121 (2.5)	4/58 (6.9)	-4.4 (-14.2, 1.6)
Level 3 (>2 g/dL dec. from baseline)	1/121 (0.8)	1/58 (1.7)	-0.9 (-8.4, 3.1)
Hemoglobin, high (g/dL)			
Level 2 (>2 g/dL inc. from baseline)	1/121 (0.8)	1/58 (1.7)	-0.9 (-8.4, 3.1)
Level 3 (>3 g/dL inc. from baseline)	0/121 (0)	0/58 (0)	0.0 (-6.2, 3.1)
Platelets, low (10 ³ cells/μL)			
Level 1 (<140)	2/121 (1.7)	0/58 (0)	1.7 (-4.6, 5.8)
Level 2 (<125)	1/121 (0.8)	0/58 (0)	0.8 (-5.4, 4.6)
Level 3 (<100)	0/121 (0)	0/58 (0)	0.0 (-6.2, 3.1)
<i>WBC Differential</i>			
Lymphocytes, low (10 ³ cells/μL)			
Level 1 (<1)	3/120 (2.5)	1/58 (1.7)	0.8 (-6.8, 5.7)
Level 2 (<0.75)	0/120 (0)	0/58 (0)	0.0 (-6.2, 3.1)
Level 3 (<0.5)	0/120 (0)	0/58 (0)	0.0 (-6.2, 3.1)
Lymphocytes, high (10 ³ cells/μL)			
Level 1 (>4)	10/120 (8.3)	4/58 (6.9)	1.4 (-8.8, 9.2)
Level 2 (>10)	0/120 (0)	0/58 (0)	0.0 (-6.2, 3.1)
Level 3 (>20)	0/120 (0)	0/58 (0)	0.0 (-6.2, 3.1)
Neutrophils, low (10 ³ cells/μL)			
Level 1 (<2)	17/120 (14.2)	3/58 (5.2)	9.0 (-1.2, 17.4)
Level 2 (<1)	1/120 (0.8)	1/58 (1.7)	-0.9 (-8.4, 3.1)
Level 3 (<0.5)	0/120 (0)	0/58 (0)	0.0 (-6.2, 3.1)
Eosinophils, high (10 ³ cells/μL)			
Level 1 (>0.65)	4/120 (3.3)	2/58 (3.4)	-0.1 (-8.7, 5.5)
Level 2 (>1.5)	0/120 (0)	1/58 (1.7)	-1.7 (-9.2, 1.4)
Level 3 (>5)	0/120 (0)	0/58 (0)	0.0 (-6.2, 3.1)
<i>Coagulation Studies</i>			
PTT, high (sec)			
Level 1 (>1× ULN)	8/121 (6.6)	4/59 (6.8)	-0.2 (-10.2, 7.2)
Level 2 (>1.21× ULN)	1/121 (0.8)	0/59 (0)	0.8 (-5.3, 4.6)
Level 3 (>1.41× ULN)	0/121 (0)	0/59 (0)	0.0 (-6.1, 3.1)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 24 weeks.

Risk difference (with 95% confidence interval) is shown between treatment and comparator.

In addition to central laboratory data, local laboratory data may be included in the analysis, if applicable.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

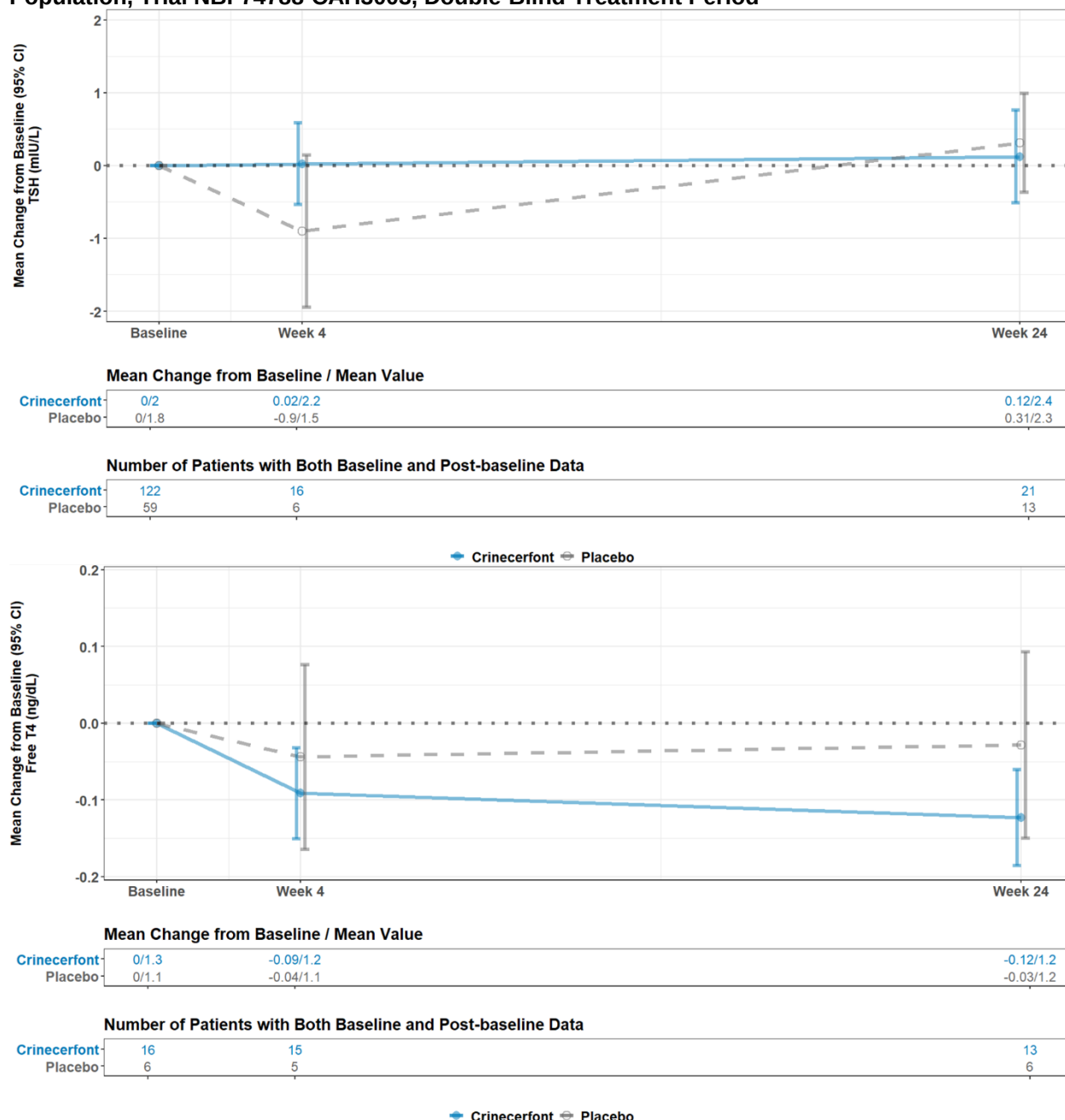
Abbreviations: CI, confidence interval; dec., decrease; inc., increase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; NA, not applicable; N_w, number of subjects with data; PT, prothrombin time; PTT, partial thromboplastin time;

ULN, upper limit of normal; WBC, white blood cell

23.2.3. Thyroid Function Tests, Trial CAH3003

There were no clinically meaningful changes in mean thyroid function test values of TSH or free T4 in either treatment group (see [Figure 77](#)).

Figure 77. Mean Thyroid Function Test Value Change From Baseline Over Time, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



Source: adlb.xpt; Software: R

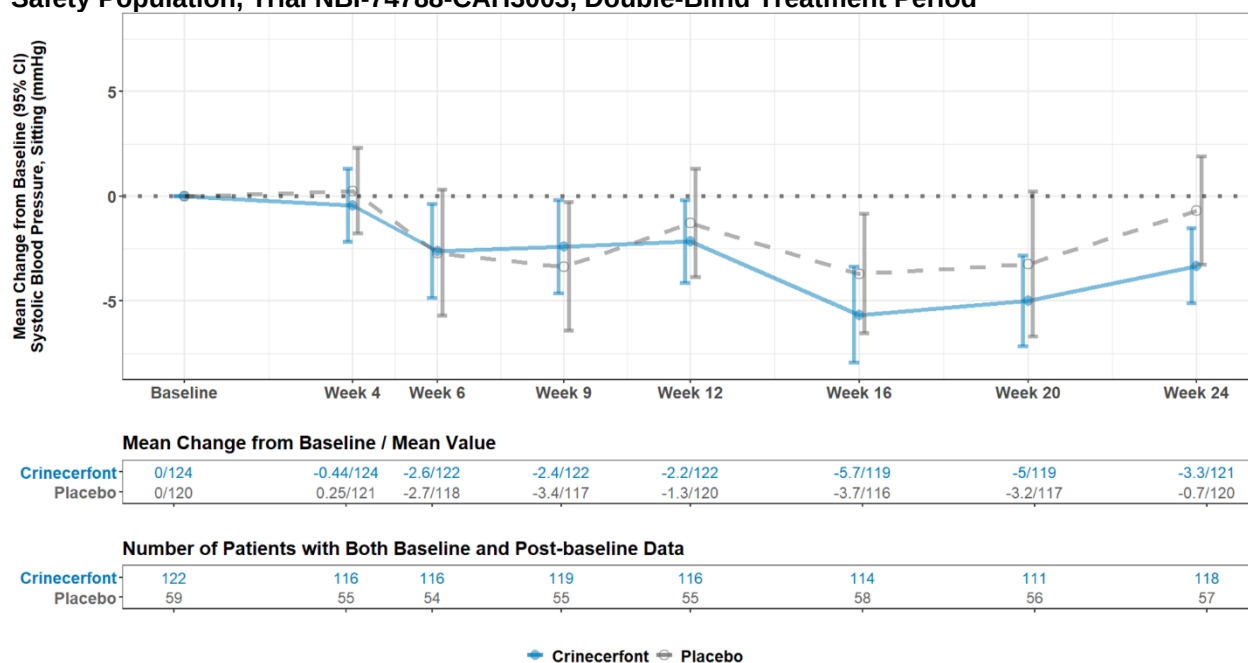
Figures do not include time points with data from fewer than 5% of randomized/enrolled subjects in all treatment groups.

Abbreviations: CI, confidence interval; T4, thyroxine; TSH, thyroid stimulating hormone

23.3. Vital Signs, Trial CAH3003

Figure 78, Figure 79, Figure 80, Figure 81, and Figure 82 show the trend in mean vital sign parameters for the two treatment groups during the double-blind treatment phase. Mean changes in both treatment groups were small and not clinically meaningful.

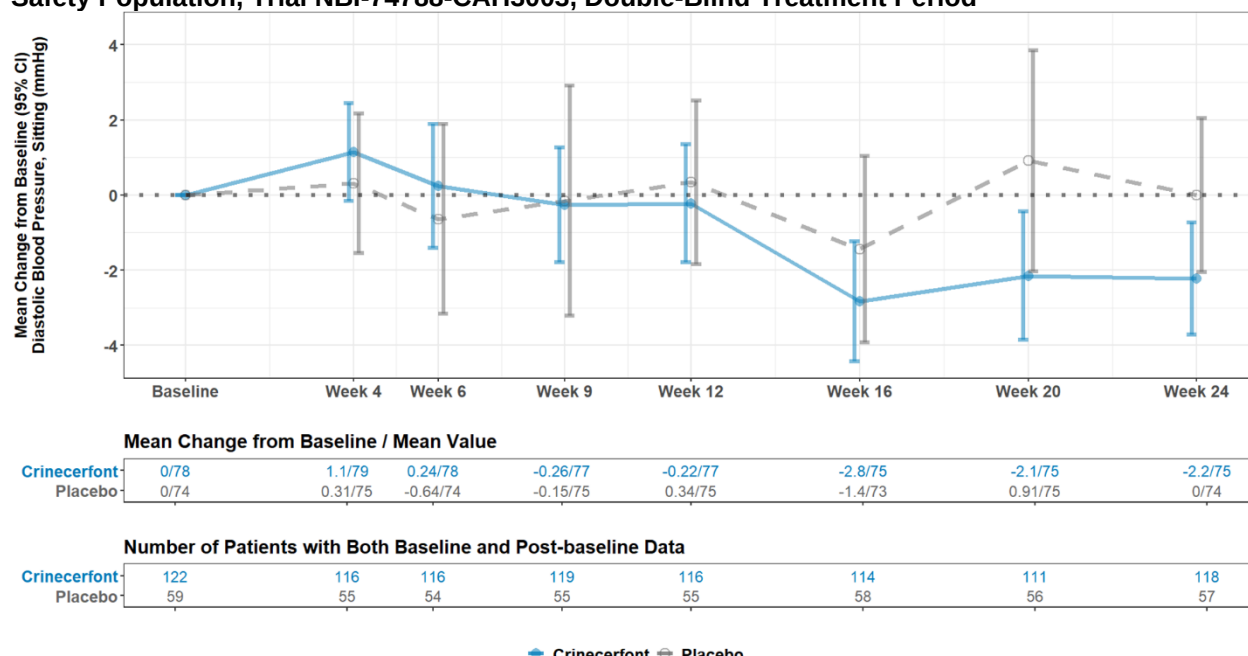
Figure 78. Mean Systolic Blood Pressure Change From Baseline Over Time by Treatment Arm, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



Source: advs.xpt; Software: R
Abbreviation: CI, confidence interval

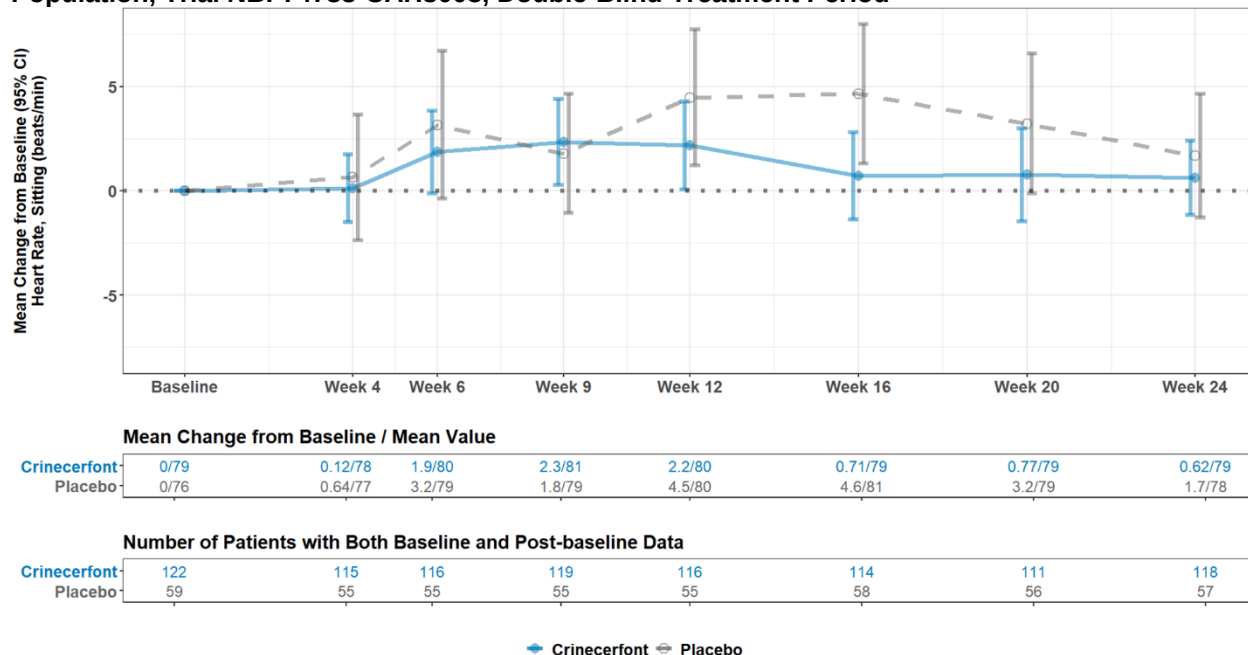
NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

Figure 79. Mean Diastolic Blood Pressure Change From Baseline Over Time by Treatment Arm, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



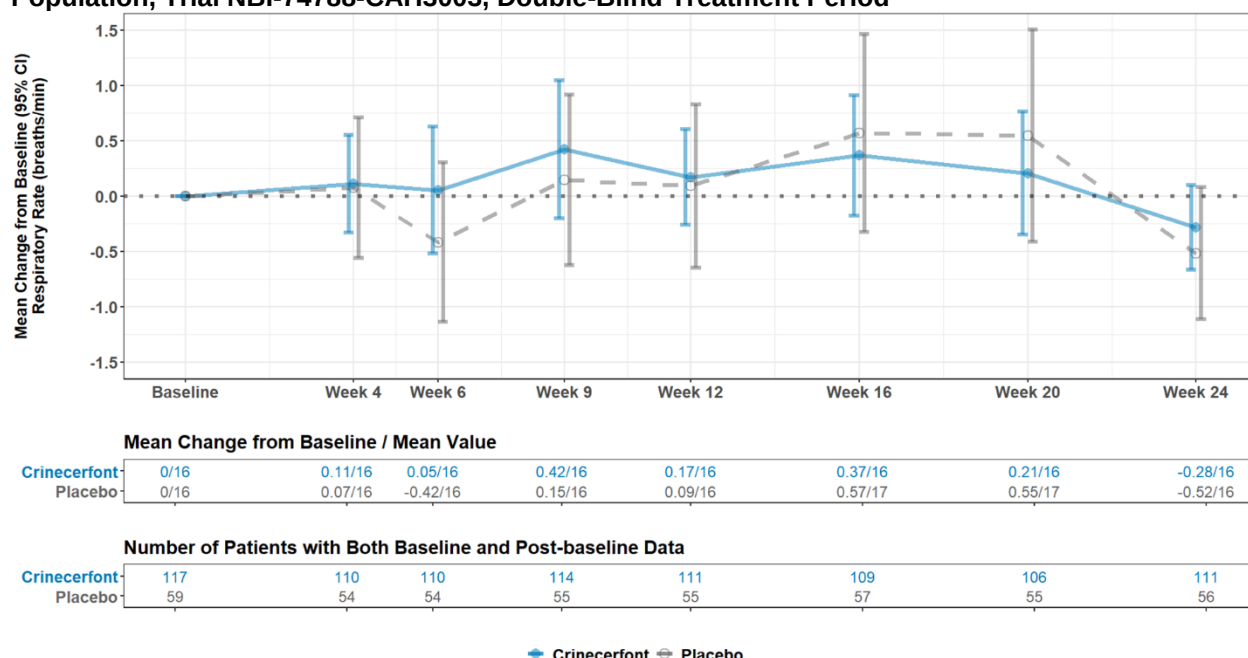
Source: advs.xpt; Software: R
Abbreviations: CI, confidence interval

Figure 80. Mean Pulse Rate Change From Baseline Over Time by Treatment Arm, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



Source: advs.xpt; Software: R
Abbreviations: CI, confidence interval

Figure 81. Mean Respiratory Rate Change From Baseline Over Time by Treatment Arm, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

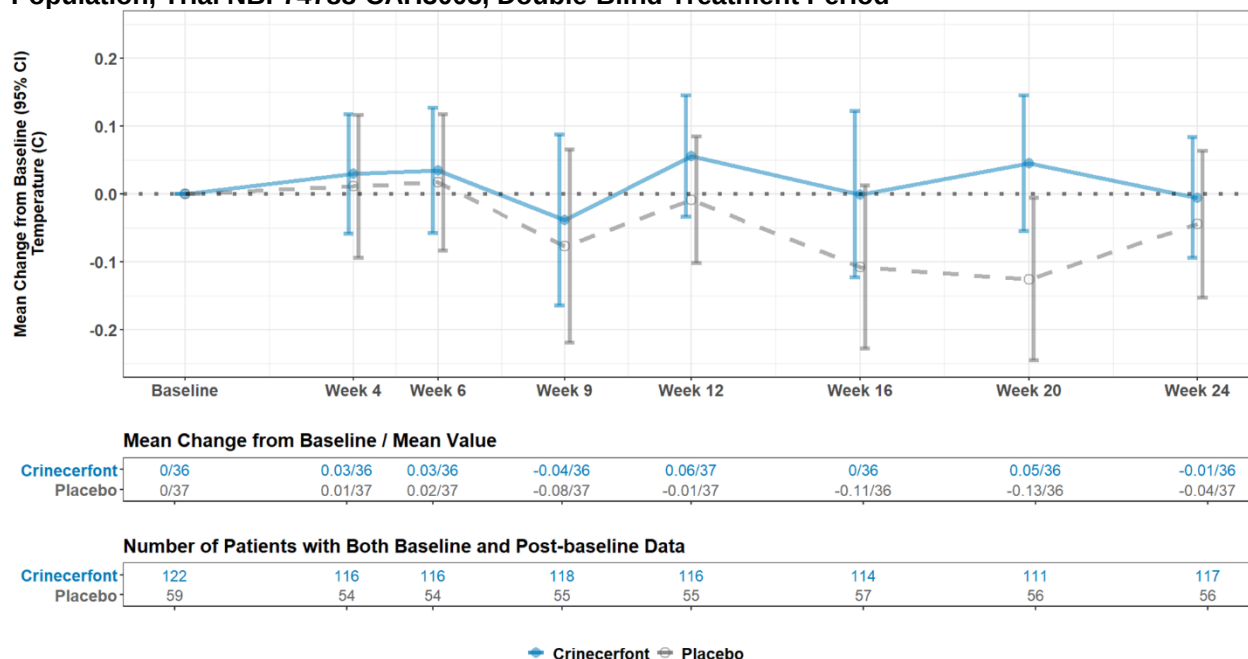


Source: advs.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.

Abbreviations: CI, confidence interval

Figure 82. Mean Body Temperature Change From Baseline Over Time by Treatment Arm, Safety Population, Trial NBI-74788-CAH3003, Double-Blind Treatment Period



Source: advs.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.

Abbreviations: CI, confidence interval

[Table 199](#) shows the proportion of subjects with orthostatic hypotension by visit. There were no meaningful differences compared to baseline in the proportion of subjects with orthostatic hypotension through Week 24.

Table 199. Subjects With Orthostatic Hypotension by Visit, Safety Analysis Set, Trial NBI-74788-CAH3003, Double-Blind Treatment Period

Parameter	Placebo (N=59)	Crinecerfont 100 mg bid (N=122)
Baseline		
Number of subjects	59	122
Decrease from sitting to standing values in diastolic BP of >10 mm Hg, n (%)	1 (1.7)	2 (1.6)
Decrease from sitting to standing values in systolic BP of >20 mm Hg, n (%)	0	10 (8.2)
Week 6		
Number of subjects	52	113
Decrease from sitting to standing values in diastolic BP of >10 mm Hg, n (%)	2 (3.8)	5 (4.4)
Decrease from sitting to standing values in systolic BP of >20 mm Hg, n (%)	0	1 (0.9)
Week 9		
Number of subjects	55	118
Decrease from sitting to standing values in diastolic BP of >10 mm Hg, n (%)	1 (1.8)	4 (3.4)
Decrease from sitting to standing values in systolic BP of >20 mm Hg, n (%)	1 (1.8)	3 (2.5)
Week 12		
Number of subjects	55	115
Decrease from sitting to standing values in diastolic BP of >10 mm Hg, n (%)	4 (7.3)	5 (4.3)
Decrease from sitting to standing values in systolic BP of >20 mm Hg, n (%)	1 (1.8)	1 (0.9)
Week 24		
Number of subjects	56	118
Decrease from sitting to standing values in diastolic BP of >10 mm Hg, n (%)	0	4 (3.4)
Decrease from sitting to standing values in systolic BP of >20 mm Hg, n (%)	0	4 (3.4)

Source: adapted from Trial NBI-74788-CAH3003 Clinical Study Report, Table 14.6.1.1.2

Orthostatic hypotension is defined as a decrease in systolic BP of >20mm Hg or a decrease in diastolic BP of >10mm Hg from sitting to standing.

Sitting blood pressure measurements are the average of triplicate values.

If a subject has multiple standing vital signs collected during the same visit, the last one collected was used to determine whether the subject met the criteria for orthostatic hypotension.

Abbreviations: bid, twice daily; BP, blood pressure

23.4. Laboratory Outlier Analysis, Trial CAH2006

23.4.1. Chemistry, Trial CAH2006

Outlier analysis tables for chemistry, renal function, and lipid parameters during the double-blind treatment period are shown in [Table 200](#), [Table 201](#), and [Table 202](#), respectively. Other than what was discussed in earlier sections of this review, there were no clinically meaningful differences in incidence of laboratory parameters outside the normal range between treatment groups.

Mean serum creatinine was stable in both treatment groups during the double-blind treatment phase ([Figure 83](#)).

Table 200. Subjects With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=69 n/N_w (%)	Placebo N=33 n/N_w (%)	Risk Difference % (95% CI)
Sodium, low (mEq/L)			
Level 1 (<132)	1/69 (1.4)	0/33 (0)	1.4 (-9.1, 7.8)
Level 2 (<130)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (<125)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Sodium, high (mEq/L)			
Level 1 (>150)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 2 (>155)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (>160)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Potassium, low (mEq/L)			
Level 1 (<3.6)	1/69 (1.4)	1/33 (3.0)	-1.6 (-14.1, 5.2)
Level 2 (<3.4)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (<3)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Potassium, high (mEq/L)			
Level 1 (>5.5)	1/69 (1.4)	0/33 (0)	1.4 (-9.1, 7.8)
Level 2 (>6)	1/69 (1.4)	0/33 (0)	1.4 (-9.1, 7.8)
Level 3 (>6.5)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Chloride, low (mEq/L)			
Level 1 (<95)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 2 (<88)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (<80)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Chloride, high (mEq/L)			
Level 1 (>108)	4/69 (5.8)	3/33 (9.1)	-3.3 (-18.4, 7.0)
Level 2 (>112)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (>115)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Bicarbonate, low (mEq/L)			
Level 1 (<20)	3/69 (4.3)	6/33 (18.2)	-13.8 (-30.6, -1.9)*
Level 2 (<18)	0/69 (0)	2/33 (6.1)	-6.1 (-19.7, -0.5)*
Level 3 (<15)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Bicarbonate, high (mEq/L)			
Level 3 (>30)	3/69 (4.3)	0/33 (0)	4.3 (-6.3, 12.1)
Glucose, low (mg/dL)			
Level 1 (<70)	5/69 (7.2)	2/33 (6.1)	1.2 (-13.1, 11.2)
Level 2 (<54)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (<40)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Glucose, fasting, high (mg/dL)			
Level 1 (≥100 to 125)	0/67 (0)	4/32 (12.5)	-12.5 (-28.2, -4.9)*
Level 2 (≥126)	0/67 (0)	0/32 (0)	0.0 (-10.8, 5.5)
Glucose, random, high (mg/dL)			
Level 2 (≥200)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (>250)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Calcium, low (mg/dL)			
Level 1 (<8.4)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 2 (<8)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (<7.5)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Calcium, high (mg/dL)			
Level 1 (>10.5)	2/69 (2.9)	2/33 (6.1)	-3.2 (-17.1, 5.2)
Level 2 (>11)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (>12)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)

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Laboratory Parameter	Crinecerfont N=69 n/N _w (%)	Placebo N=33 n/N _w (%)	Risk Difference % (95% CI)
Magnesium, low (mg/dL)			
Level 1 (<1.5)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 2 (<1.2)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (<0.9)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Magnesium, high (mg/dL)			
Level 1 (>2.3)	3/69 (4.3)	2/33 (6.1)	-1.7 (-15.8, 7.3)
Level 2 (>4)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (>7)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Phosphate, low (mg/dL)			
Level 1 (<2.5)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 2 (<2)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (<1.4)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Protein, total, low (g/dL)			
Level 1 (<6)	1/69 (1.4)	1/33 (3.0)	-1.6 (-14.1, 5.2)
Level 2 (<5.4)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (<5)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Albumin, low (g/dL)			
Level 1 (<3.1)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 2 (<2.5)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
Level 3 (<2)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)
CPK, high (U/L)			
Level 1 (>3× ULN)	1/69 (1.4)	1/33 (3.0)	-1.6 (-14.1, 5.2)
Level 2 (>5× ULN)	1/69 (1.4)	0/33 (0)	1.4 (-9.1, 7.8)
Level 3 (>10× ULN)	1/69 (1.4)	0/33 (0)	1.4 (-9.1, 7.8)
Blood urea nitrogen, high (mg/dL)			
Level 1 (>23)	1/69 (1.4)	1/33 (3.0)	-1.6 (-14.1, 5.2)
Level 2 (>27)	0/69 (0)	1/33 (3.0)	-3.0 (-15.4, 2.4)
Level 3 (>31)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)

Source: adlb.xpt; Software: R

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; CPK, creatine phosphokinase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data; ULN, upper limit of normal

Table 201. Subjects With One or More Kidney Function Analyte Values Exceeding Specified Levels, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=69 n/N _w (%)	Placebo N=33 n/N _w (%)	Risk Difference % (95% CI)
Creatinine, high (mg/dL)			
Level 1 (≥1.5× baseline)	0/69 (0)	2/33 (6.1)	-6.1 (-19.7, -0.5)*
Level 2 (≥2× baseline)	0/69 (0)	1/33 (3.0)	-3.0 (-15.4, 2.4)
Level 3 (≥3× baseline)	0/69 (0)	0/33 (0)	0.0 (-10.5, 5.3)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 28 weeks.

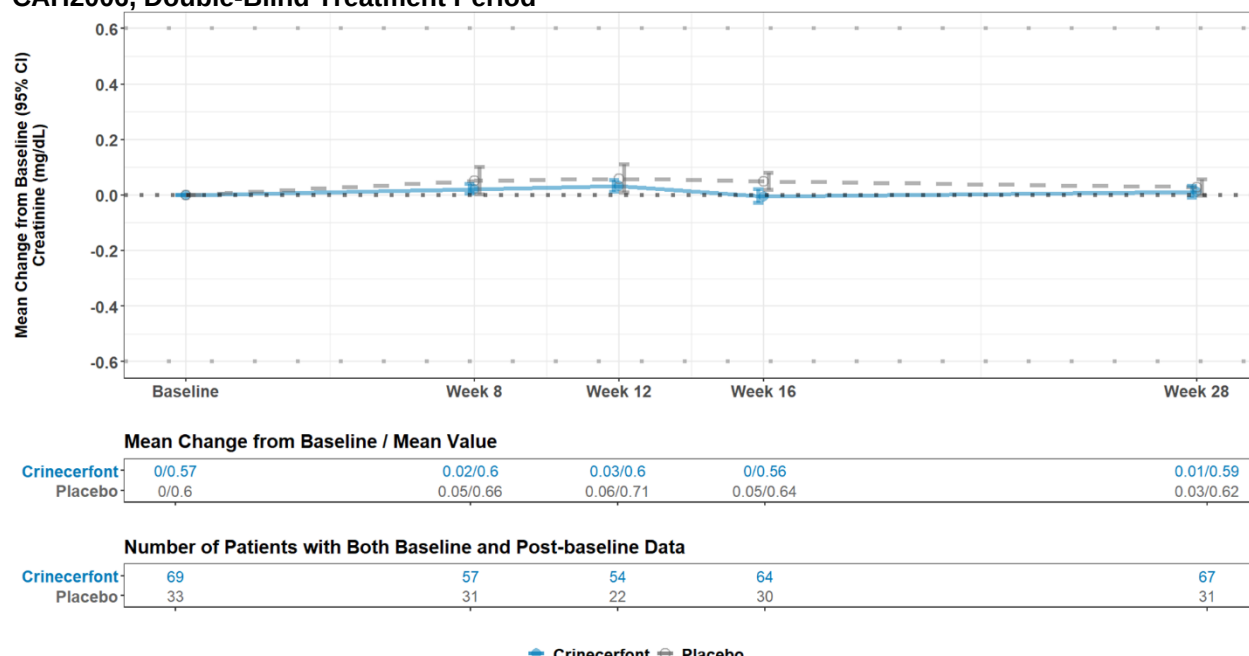
Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

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Figure 83. Mean Creatinine Change From Baseline Over Time, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period



Source: adlb.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.

Abbreviations: CI, confidence interval

Table 202. Subjects With One or More Lipids Analyte Values Exceeding Specified Levels, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=69 n/N _w (%)	Placebo N=33 n/N _w (%)	Risk Difference % (95% CI)
Cholesterol, total, high (mg/dL)			
Level 1 (>200)	7/67 (10.4)	4/32 (12.5)	-2.1 (-18.8, 10.4)
Level 2 (>210)	5/67 (7.5)	2/32 (6.2)	1.2 (-13.5, 11.5)
Level 3 (>225)	1/67 (1.5)	0/32 (0)	1.5 (-9.4, 8.0)
HDL, males, low (mg/dL)			
Level 1 (<40)	8/35 (22.9)	3/17 (17.6)	5.2 (-21.3, 26.2)
Level 2 (<30)	0/35 (0)	0/17 (0)	0.0 (-18.7, 10.1)
Level 3 (<20)	0/35 (0)	0/17 (0)	0.0 (-18.7, 10.1)
HDL, females, low (mg/dL)			
Level 1 (<50)	14/32 (43.8)	7/15 (46.7)	-2.9 (-32.2, 26.0)
Level 2 (<40)	7/32 (21.9)	4/15 (26.7)	-4.8 (-33.4, 19.3)
Level 3 (<20)	0/32 (0)	0/15 (0)	0.0 (-20.7, 10.9)
LDL, high (mg/dL)			
Level 1 (>130)	7/67 (10.4)	1/32 (3.1)	7.3 (-6.2, 17.7)
Level 2 (>160)	0/67 (0)	0/32 (0)	0.0 (-10.8, 5.5)
Level 3 (>190)	0/67 (0)	0/32 (0)	0.0 (-10.8, 5.5)

Laboratory Parameter	Crinecerfont N=69 n/N_w (%)	Placebo N=33 n/N_w (%)	Risk Difference % (95% CI)
Triglycerides, high (mg/dL)			
Level 1 (>150)	3/67 (4.5)	2/32 (6.2)	-1.8 (-16.2, 7.5)
Level 2 (>300)	1/67 (1.5)	0/32 (0)	1.5 (-9.4, 8.0)
Level 3 (>500)	0/67 (0)	0/32 (0)	0.0 (-10.8, 5.5)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; N, number of subjects in treatment arm; n, number of subjects meeting criteria; N_w, number of subjects with data

23.4.2. Hematology, Trial CAH2006

Other than what was discussed in earlier sections of this review regarding neutrophil and white blood cell counts, there were no clinically meaningful differences between crinecerfont and placebo groups in incidence of hematology parameters outside the normal range or in mean change from baseline in hemoglobin, hematocrit, or platelet count.

Table 203. Subjects With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

Laboratory Parameter	Crinecerfont N=69 n/N_w (%)	Placebo N=33 n/N_w (%)	Risk Difference % (95% CI)
<i>Complete Blood Count</i>			
WBC, low (10 ³ cells/μL)			
Level 1 (<3.5)	1/68 (1.5)	0/32 (0)	1.5 (-9.4, 7.9)
Level 2 (<3)	0/68 (0)	0/32 (0)	0.0 (-10.8, 5.4)
Level 3 (<1)	0/68 (0)	0/32 (0)	0.0 (-10.8, 5.4)
WBC, high (10 ³ cells/μL)			
Level 1 (>10.8)	3/68 (4.4)	2/32 (6.2)	-1.8 (-16.2, 7.3)
Level 2 (>13)	0/68 (0)	1/32 (3.1)	-3.1 (-15.8, 2.4)
Level 3 (>15)	0/68 (0)	1/32 (3.1)	-3.1 (-15.8, 2.4)
Hemoglobin, low (g/dL)			
Level 2 (>1.5 g/dL dec. from baseline)	4/68 (5.9)	1/32 (3.1)	2.8 (-10.4, 11.8)
Level 3 (>2 g/dL dec. from baseline)	0/68 (0)	0/32 (0)	0.0 (-10.8, 5.4)
Hemoglobin, high (g/dL)			
Level 2 (>2 g/dL inc. from baseline)	1/68 (1.5)	0/32 (0)	1.5 (-9.4, 7.9)
Level 3 (>3 g/dL inc. from baseline)	0/68 (0)	0/32 (0)	0.0 (-10.8, 5.4)
Platelets, low (10 ³ cells/μL)			
Level 1 (<140)	1/68 (1.5)	0/32 (0)	1.5 (-9.4, 7.9)
Level 2 (<125)	1/68 (1.5)	0/32 (0)	1.5 (-9.4, 7.9)
Level 3 (<100)	0/68 (0)	0/32 (0)	0.0 (-10.8, 5.4)
<i>WBC Differential</i>			
Lymphocytes, low (10 ³ cells/μL)			
Level 1 (<1)	0/68 (0)	0/32 (0)	0.0 (-10.8, 5.4)
Level 2 (<0.75)	0/68 (0)	0/32 (0)	0.0 (-10.8, 5.4)
Level 3 (<0.5)	0/68 (0)	0/32 (0)	0.0 (-10.8, 5.4)
Lymphocytes, high (10 ³ cells/μL)			
Level 1 (>4)	12/68 (17.6)	9/32 (28.1)	-10.5 (-29.6, 6.2)
Level 2 (>10)	0/68 (0)	0/32 (0)	0.0 (-10.8, 5.4)
Level 3 (>20)	0/68 (0)	0/32 (0)	0.0 (-10.8, 5.4)

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Laboratory Parameter	Crinecerfont N=69 n/N_w (%)	Placebo N=33 n/N_w (%)	Risk Difference % (95% CI)
Neutrophils, low (10 ³ cells/μL)			
Level 1 (<2)	25/68 (36.8)	5/32 (15.6)	21.1 (2.0, 36.7)*
Level 2 (<1)	3/68 (4.4)	0/32 (0)	4.4 (-6.6, 12.2)
Level 3 (<0.5)	1/68 (1.5)	0/32 (0)	1.5 (-9.4, 7.9)
Eosinophils, high (10 ³ cells/μL)			
Level 1 (>0.65)	7/68 (10.3)	4/32 (12.5)	-2.2 (-18.9, 10.2)
Level 2 (>1.5)	0/68 (0)	1/32 (3.1)	-3.1 (-15.8, 2.4)
Level 3 (>5)	0/68 (0)	0/32 (0)	0.0 (-10.8, 5.4)
<i>Coagulation Studies</i>			
PTT, high (sec)			
Level 1 (>1× ULN)	7/69 (10.1)	1/32 (3.1)	7.0 (-6.5, 17.1)
Level 2 (>1.21× ULN)	1/69 (1.4)	0/32 (0)	1.4 (-9.4, 7.8)
Level 3 (>1.41× ULN)	0/69 (0)	0/32 (0)	0.0 (-10.8, 5.3)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 28 weeks.

Risk difference (with 95% confidence interval) is shown between total treatment and comparator.

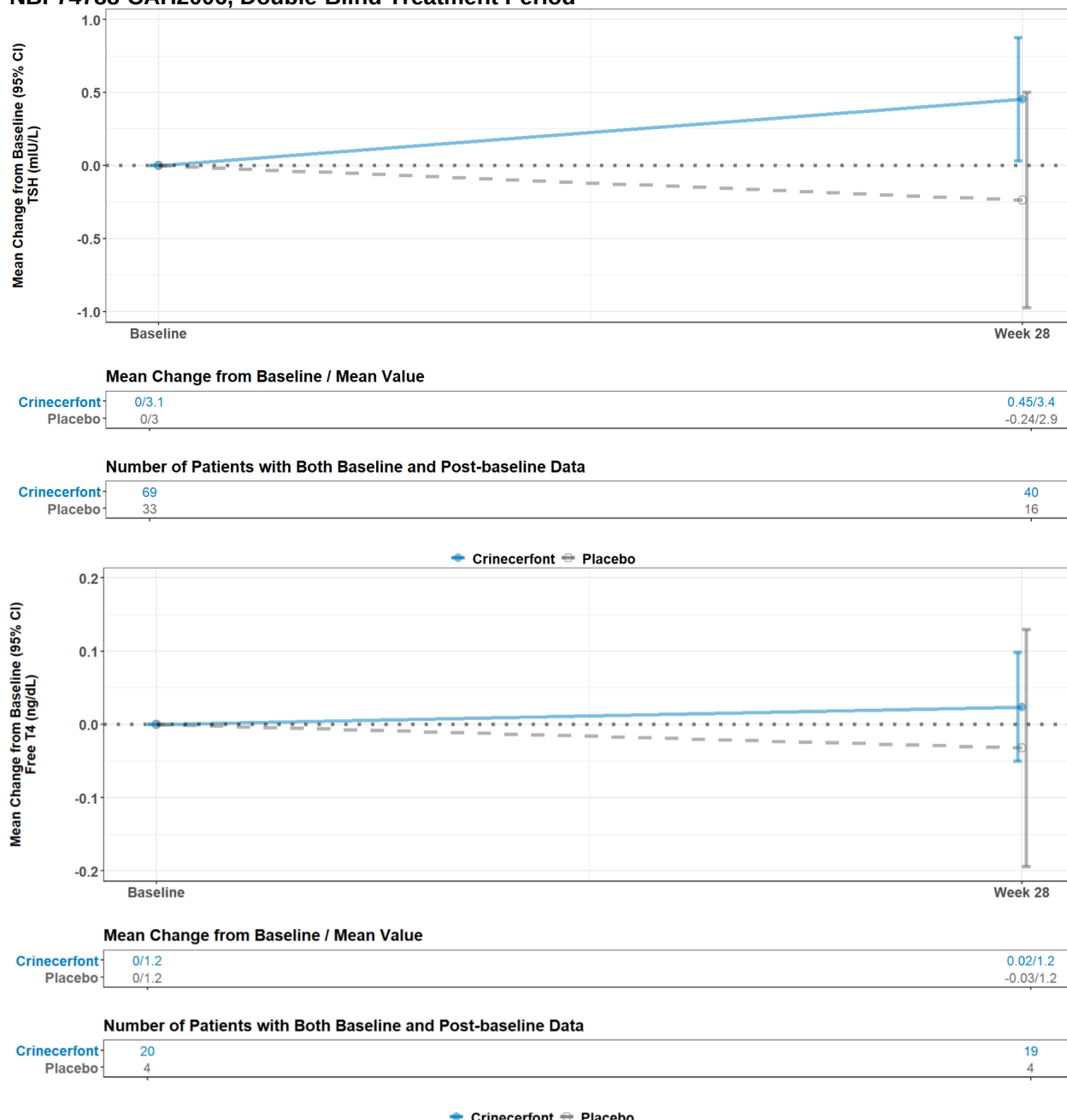
Asterisk (*) indicates rows where the 95% confidence interval excludes zero.

Abbreviations: CI, confidence interval; dec., decrease; inc., increase; N, number of subjects in treatment arm; n, number of subjects meeting criteria; NA, not applicable; N_w, number of subjects with data; PT, prothrombin time; PTT, partial thromboplastin time; ULN, upper limit of normal; WBC, white blood cell

23.4.3. Thyroid Function Tests, Trial CAH2006

There were no clinically meaningful changes in mean thyroid function test values of TSH or free T4 in either treatment group as shown in [Figure 84](#).

Figure 84. Mean Change From Baseline in TSH and Free T4 Over Time, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period



Source: adlb.xpt; Software: R

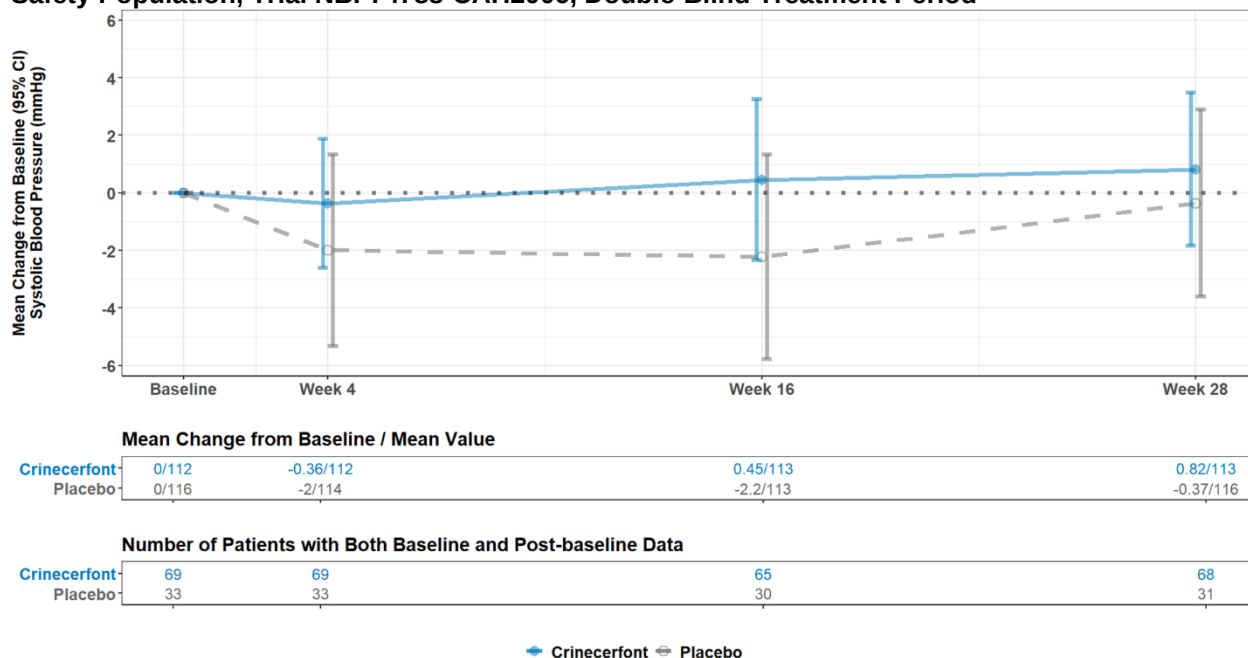
Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.

Abbreviations: CI, confidence interval; T4, thyroxine; TSH, thyroid stimulating hormone

23.5. Vital Signs, Trial CAH2006

Figure 85, Figure 86, Figure 87, Figure 88, and Figure 89 show the trend in mean vital sign parameters (systolic blood pressure, diastolic blood pressure, heart rate, respiratory rate, and temperature) for the two treatment groups during the double-blind treatment phase. Mean changes in both treatment groups were small and not clinically meaningful.

Figure 85. Mean Systolic Blood Pressure Change From Baseline Over Time by Treatment Arm, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

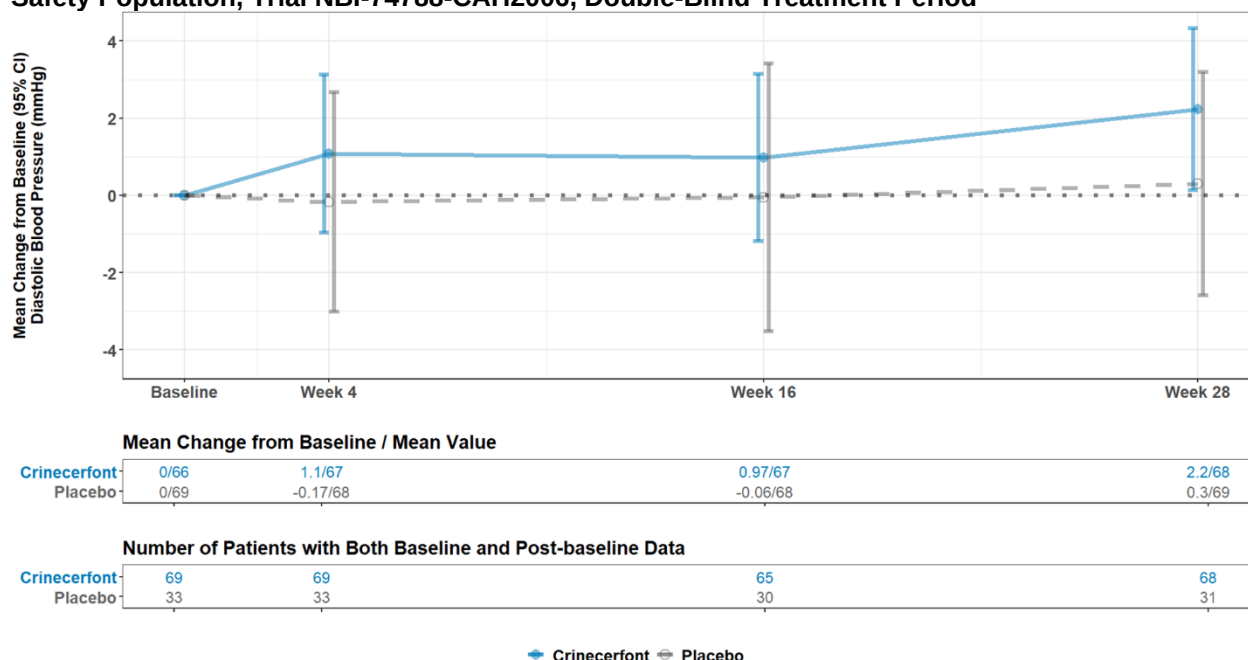


Source: advs.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.

Abbreviations: CI, confidence interval

Figure 86. Mean Diastolic Blood Pressure Change From Baseline Over Time by Treatment Arm, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

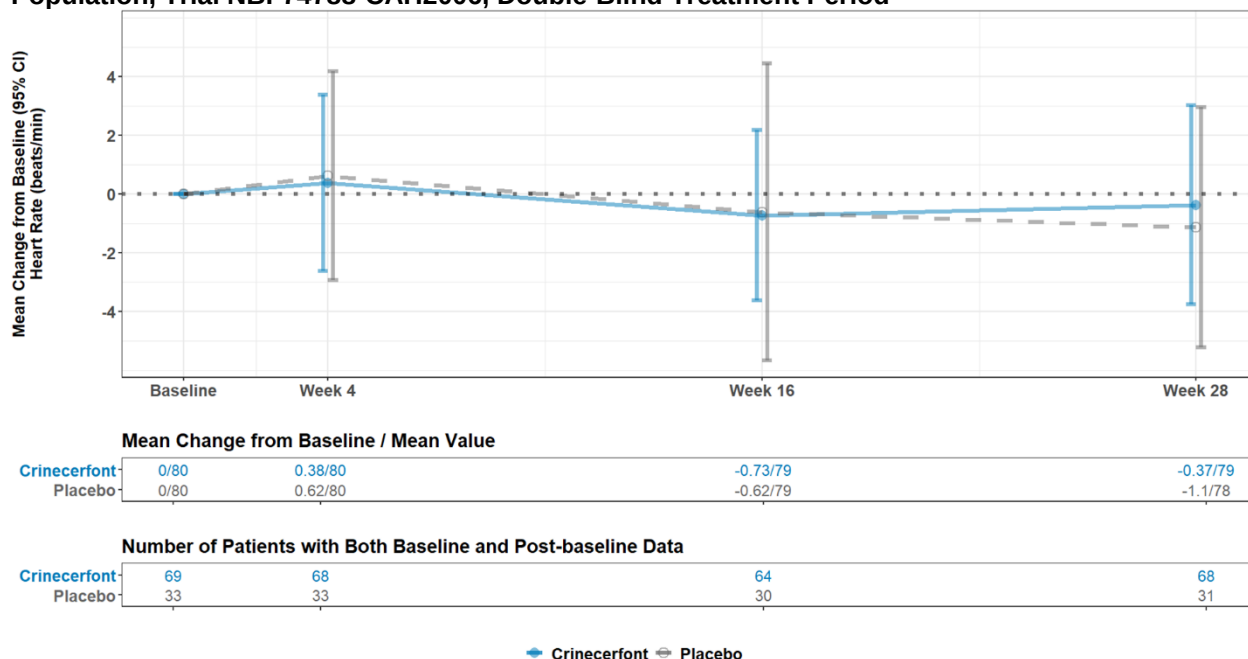


Source: advs.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.

Abbreviations: CI, confidence interval

Figure 87. Mean Pulse Rate Change From Baseline Over Time by Treatment Arm, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

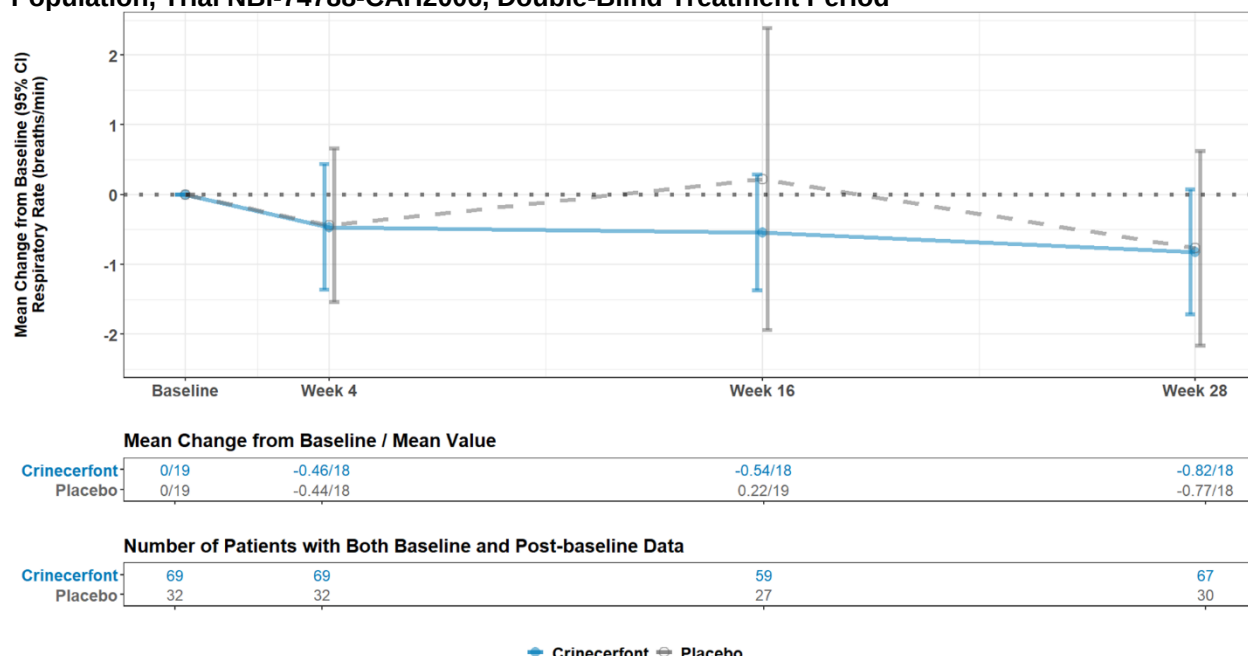


Source: advs.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.

Abbreviations: CI, confidence interval

Figure 88. Mean Respiratory Rate Change From Baseline Over Time by Treatment Arm, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period

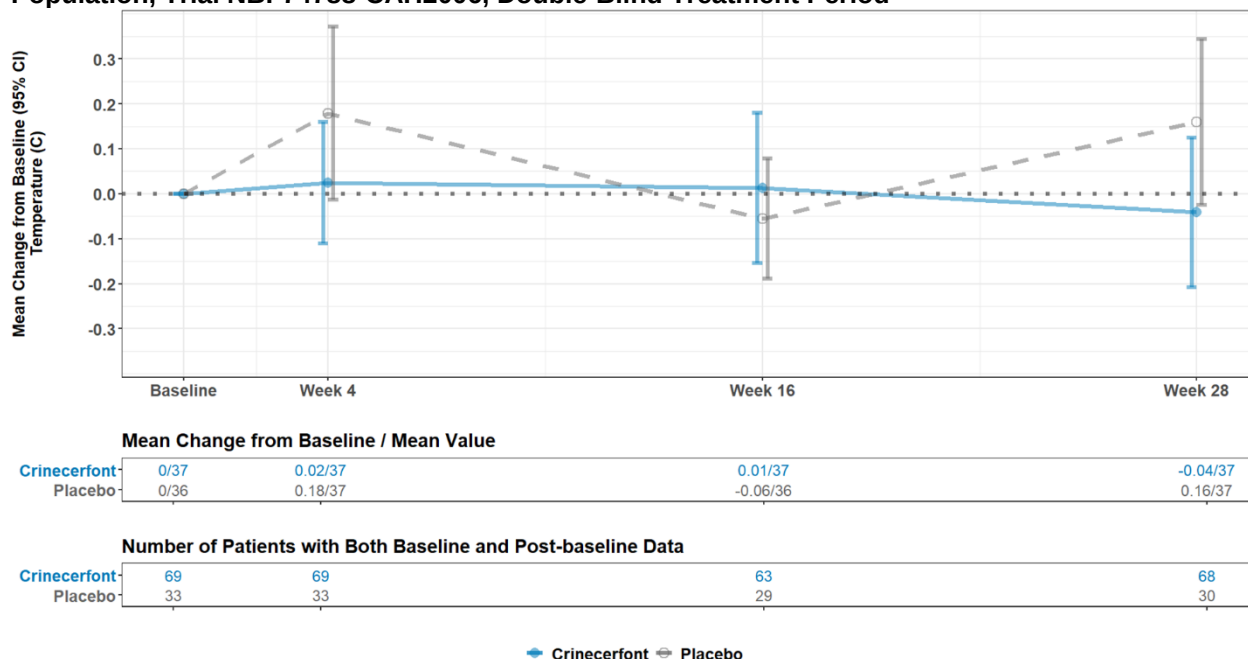


Source: advs.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.

Abbreviations: CI, confidence interval

Figure 89. Mean Body Temperature Change From Baseline Over Time by Treatment Arm, Safety Population, Trial NBI-74788-CAH2006, Double-Blind Treatment Period



Source: advs.xpt; Software: R

Figures do not include time points with data from fewer than 10% of randomized/enrolled subjects in all treatment groups.

Abbreviations: CI, confidence interval

24. Clinical Virology

Not applicable.

25. Clinical Microbiology

Not applicable.

26. Mechanism of Action/Drug Resistance

Not applicable.

27. Other Drug Development Considerations

The Division of Medication Error Prevention and Analysis 1 (DMEPA 1) concluded that the proposed proprietary name, CRENESSITY, is conditionally acceptable.³³

DMEPA 1 also reviewed the proposed CRENESSITY prescribing information (PI), patient prescribing information, and container labels for areas of vulnerability that may lead to medication errors and provided recommendations to minimize the risk for medication error.³⁴ Labeling changes are discussed in detail in Section [29](#).

28. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

The Office of Scientific Investigations was consulted for these NDAs and conducted inspections for the following three study sites that were involved in both protocol NBI-74788-CAH2006 and protocol NBI-74788-CAH3003:

- Dr. Eric Felner, Atlanta, Georgia: No objectionable conditions or practices that would justify enforcement action by the Office of Compliance.
- Dr. Mimi Kim, Children’s Hospital Los Angeles, Los Angeles, California: No objectionable conditions or practices that would justify enforcement action by the Office of Compliance.
- Dr. Oksana Hamidi, University of Texas Southwestern Medical Center, Dallas, Texas: No objectionable conditions or practices that would justify enforcement action by the Office of Compliance.

Based on the overall inspection results of these three sites and the regulatory assessments, the Office of Scientific Investigations concludes that data generated by these three investigators and

³³ DMEPA memorandum filed to NDA 218808 in DARRTS dated July 15, 2024.

³⁴ DMEPA memorandum filed to NDA 218808 in DARRTS dated September 24, 2024.

NDA 218808 and NDA 218820
CRENESSITY (crinecerfont) oral capsule and oral solution

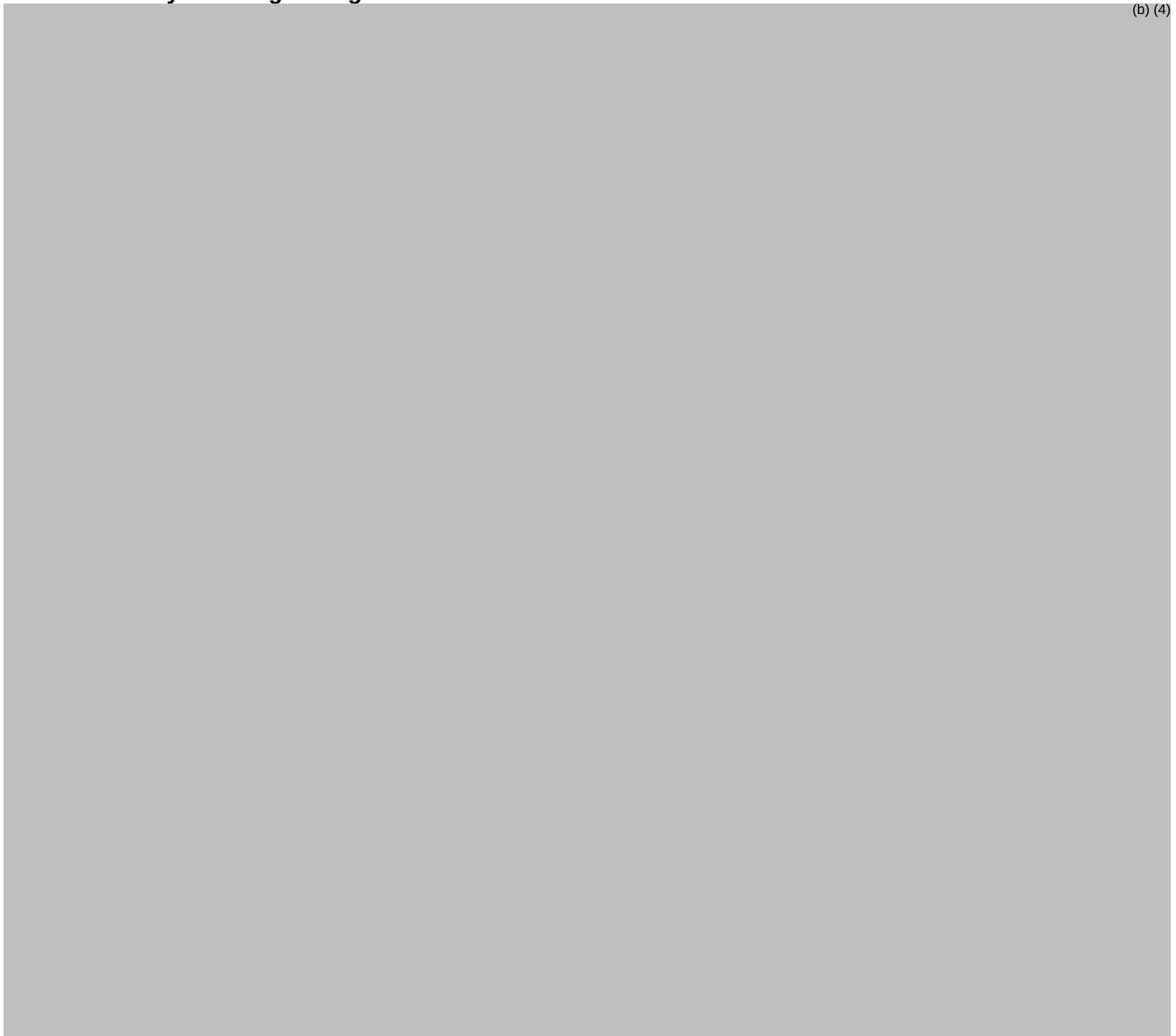
submitted by the Applicant are verifiable. Trials CAH2006 and CAH3003 appear to have been conducted adequately and the clinical data submitted by the Applicant appear acceptable in support of the respective indication.

29. Labeling: Key Changes

This PI review includes a high-level summary of the rationale for major changes to the finalized PI as compared to the Applicant's draft PI. The PI was reviewed to ensure that it meets regulatory/statutory requirements, is consistent (if appropriate) with labeling guidance, conveys clinically meaningful and scientifically accurate information needed for the safe and effective use of the drug, and provides clear and concise information for the healthcare practitioner.

Table 204. Key Labeling Changes and Considerations

(b) (4)



29.1. Approved Labeling Types

Upon approval of this application, the following labeling documents will be FDA-approved:

- Prescribing information
- Patient information
- Instructions for use (for the oral solution)

30. Postmarketing Requirements and Commitments

The review team is concerned about a serious risk of inhibition of ACTH secretion in the developing fetus, which may lead to fetal growth restriction, preterm delivery, or demise, and to an unexpected serious risk of infant exposure to crinecerfont during lactation. The Division of Pediatrics and Maternal Health (DPMH) in a memorandum of consultation filed to NDA 218808 in DARRTS on September 13, 2024, recommends a postmarketing requirement (PMR) for a descriptive pregnancy safety study (DPSS) for the following reasons:

- Three pregnancies occurred during the drug development program, indicating that females of reproductive potential with classic CAH may take crinecerfont. Although there were pregnancies that occurred during drug development, there are no data from these pregnancies to inform the use of crinecerfont during pregnancy. Thus, a DPSS would provide necessary pregnancy safety data.
- Given that classic CAH is a rare disease, the number of pregnant patients who use crinecerfont is likely to be small. With a small number of pregnant patients using crinecerfont, a pregnancy exposure registry would be unlikely to adequately enroll patients; therefore, a DPSS is preferred.
- Crinecerfont is systemically absorbed and will cross the placenta. Crinecerfont has the potential to inhibit ACTH secretion in the developing fetus, thereby reducing cortisol levels in the fetus, which may result in fetal growth restriction, preterm delivery, or demise.

DPMH also recommends a PMR for a clinical lactation study to determine the extent to which crinecerfont is present in human milk. Their rationale is that crinecerfont is present in animal milk, which presents a potential for adrenal insufficiency or crisis in healthy neonates and infants exposed to crinecerfont via breast milk.

The following are postmarketing requirements to assess the effect of crinecerfont on developing fetuses and lactation:

- Conduct a worldwide descriptive study that collects prospective and retrospective data in women exposed to crinecerfont during pregnancy and/or lactation to assess risk of pregnancy and maternal complications, adverse effects on the developing fetus and neonate, and adverse effects on the infant. Infant outcomes will be assessed through at least the first year of life. The minimum number of patients will be specified in the protocol.

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- Perform a lactation study (milk only or mother-infant pair study) in lactating women who have received crinecerfont to measure concentrations of crinecerfont and its major metabolites in breast milk using a validated assay and to assess the effects on the breastfed infant, if available, based on study population.

DGE discussed advice from the Division of Pharmacovigilance in the Office of Surveillance and Epidemiology regarding further assessment of suicidality and neutropenia in the postmarket setting. The Division of Pharmacovigilance recommends the Applicant commit to the following enhanced pharmacovigilance plan:

- Neutropenia
 - Submit all serious and non-serious domestic and/or foreign cases of neutropenia as 15-day “alert reports”) through the 5th year following initial U.S. approval.
 - Include narrative summary analyses of events of neutropenia in the required periodic safety reports through the 5th year following initial U.S. approval. Use the Medical Dictionary for Regulatory Activities (MedDRA) high-level term (HLT) “neutropenias” to retrieve reports.
- Suicidality
 - Submit all serious and non-serious domestic and/or foreign cases of suicidal behavior and/or ideation as 15-day “alert reports” through the 5th year following initial U.S. approval.
 - Include narrative summary analyses of suicidal behavior and/or ideation in the required periodic safety reports through the 5th year following initial U.S. approval. Use the MedDRA preferred terms (PTs) of “completed suicide,” “suicide attempt,” “suicidal behavior,” and “suicidal ideation” to retrieve reports.

Narrative summary analyses of neutropenia and suicidality in the periodic safety reports should include interval and cumulative data relative to the date of approval of CRENESSITY (crinecerfont) and should provide an assessment of causality, with documentation of indication, temporal association, duration of therapy, associated signs and symptoms, confounders, underlying risk factors (e.g., psychiatric history), treatment given for the event, outcome, and drug disposition.

31. Financial Disclosure

Table 205. Covered Clinical Studies: Trial NBI-74788-CAH3003 and Trial NBI-74788-CAH2006

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 353		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: Enter text here. Significant payments of other sorts: Enter text here. Proprietary interest in the product tested held by investigator: Enter text here. Significant equity interest held by investigator: Enter text here. Sponsor of covered study: Enter text here.		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

32. References

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Guidance Documents

(b) (4)

Draft guidance for industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products* (December 2019)

Guidance for industry *Clinical Drug Interaction Studies With Combined Oral Contraceptives Guidance for Industry* (June 2023)

Guidance for industry *Pharmacokinetics in Patients with Impaired Renal Function* (March 2024)

Guidance for industry *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products* (May 1998)

ICH guideline *M12 Drug Interaction Studies* (May 2024)

(b) (4)

Guidance for industry *Demonstrating Substantial Evidence of Effectiveness With One Adequate and Well-Controlled Clinical Investigation and Confirmatory Evidence* (September 2023)

Committee Reports

FAO Nutrition Meetings Report Series *Seventeenth Report of the Joint FAO/WHO Expert Committee on Food Additives: Propylene Glycol Esters of Fatty Acids* (Joint FAO/WHO Expert Committee on Food Additives 1974)

33. Review Team

Table 206. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Dana Smith
Nonclinical reviewer	Mekonnen LemmaDechassa
Nonclinical team leader	Dave Carlson
OCP reviewer(s)	Deepa Rao
OCP team leader(s)	Li Li
Clinical reviewer	Karen Vogt
Clinical team leader	Olivia Easley
Biometrics reviewer	Satyajit Ghosh
Biometrics team leader	Feng Li
Cross-discipline team leader	Olivia Easley
Division director (pharm/tox)	Todd Bourcier
Division director (OCP)	Jayabharathi Vaidyanathan
Division director (OB)	N/A
Division director (clinical)	Theresa Kehoe
Office director (or designated signatory authority)	Hylton Joffe

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics; N/A, not applicable

Table 207. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Akm Khairuzzaman / Mohan Sapru
Microbiology	Jianli Xue / Nandini Bhattacharya
OPDP	Charuni Shah
OSI	Ling Yang / Min Lu
OSE/DEPI	Po Yin Chang / Yandong Qiang
OSE/DMEPA	Peggy Rahbani / Yevgeniya (Jen) Kogan
OSE/DRISK	Theresa Ng / Yasmeen Abou-Sayed
Other	OCP/Pharmacometrics: Jiajun (JJ) Liu / Justin Earp OSE/DPV: Amy Chen / Ali Niak / Dan Woronow OPQ/Drug Substance: Stephanie Springer / Zhengfu Wang OPQ/Drug Product: George Ward / Akm Khairuzzaman OPQ/Drug Product: Jennifer McCord / Akm Khairuzzaman OPQ/BioPharm: Rajesh Savkur / Haritha Mandula OPQ/Facility and Process: Kejun Cheng / Aditi Thakur OPQ/Facility and Process: Laurie Nelson / Sateesh Sathigari OPQ/ORA: Jennifer Lalama Maternal Health (DPMH): Katherine Kratz / Miriam Dinatale Patient Labeling: Nyedra Booker / Marcia Williams CSS: Yohanka Caro / Chad Reissig Clinical Data Scientist (CDS): Megan L. Peach / Qunshu Zhang OND Policy: Sara Stradley OND Program OPO: Cathryn Lee / Pinky Patel ADL: LaiMing Lee

Abbreviations: ADL, associate director for labeling; CSS, controlled substance staff; OCP, Office of Clinical Pharmacology; OND, Office of New Drugs; OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OPO, Program Operations; ORA, Office of Regulatory Affairs; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DPMH, Department of Pediatrics and Maternal Health; DPV, Division of Pharmacovigilance; DRISK, Division of Risk Management

33.1. Reviewer Signatures

Table 33-208 Signatures of Reviewers

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Olivia Easley OCHEN DGE	Sections: 1, 2, 3, 4, 6, 7, 8, 10, 11, 12, 15, 16, 17, 21, 22, 23, 24, 25	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Olivia Easley		Digitally signed by Olivia Easley		
		Date: 12/13/2024 1:59 PM EST GUID: 20241213185943		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Primary Reviewer	Lai Lee OCHEN DGE	Sections: 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Lai Lee		Digitally signed by Lai Lee		
		Date: 12/13/2024 2:00 PM EST GUID: 2024121319050		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Secondary Reviewer	Feng Li OB DBII	Sections: Section 6	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Feng Li		Digitally signed by Feng Li		
		Date: 12/13/2024 2:02 PM EST GUID: 2024121319214		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Secondary Reviewer	Olivia Easley OCHEN DGE	Sections: 1, 2, 3, 4, 6, 7,8, , 9-12, 15-17, 21- 25	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Olivia Easley		Digitally signed by Olivia Easley		
		Date: 12/13/2024 2:02 PM EST GUID: 2024121319216		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Associate Director for Labeling Discipline Secondary Reviewer	Olivia Easley OCHEN DGE	Sections: 23	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Olivia Easley		Digitally signed by Olivia Easley		
		Date: 12/13/2024 2:03 PM EST GUID: 2024121319318		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Biostatistics Discipline Primary Reviewer	Satyajit Ghosh OB DBII	Sections: 6, 16	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Satyajit Ghosh		Digitally signed by Satyajit Ghosh		
		Date: 12/13/2024 2:09 PM EST GUID: 2024121319956		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Primary Reviewer	Dana Smith ORO DROCHEN	Sections: 12	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Dana Smith Digitally signed by Dana Smith Date: 12/13/2024 2:11 PM EST GUID: 20241213191120				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Discipline Primary Reviewer	Karen Vogt OCHEN DGE	Sections: 2, 3, 4, 6, 7, 15, 16, 17	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Karen Vogt Digitally signed by Karen Vogt Date: 12/13/2024 2:13 PM EST GUID: 20241213191316				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Secondary Reviewer	Akm Khairuzzaman OPQAI DPQAI	Sections: 9, 23	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Akm Khairuzzaman Digitally signed by Akm Khairuzzaman Date: 12/13/2024 2:25 PM EST GUID: 20241213192528				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Regulatory Project Manager Discipline Secondary Reviewer	Elisabeth Hanan ORO DROCHEN	Sections: 12	Based on my assessment of the application: ☐ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☒ Not applicable.	
Signature: Elisabeth Hanan Digitally signed by Elisabeth Hanan Date: 12/13/2024 2:29 PM EST GUID: 20241213192956				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Tertiary Reviewer	Todd Bourcier OCHEN DPTCHEN	Sections: 5, 7, 8, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	Nonclinical supports AP

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Todd Bourcier Digitally signed by Todd Bourcier Date: 12/13/2024 2:43 PM EST GUID: 20241213194348				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Deepa Rao OCP DCEP	Sections: IRT Sections 5, 6, 8 and 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: Deepa Rao Digitally signed by Deepa Rao Date: 12/13/2024 2:46 PM EST GUID: 2024121319464				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Primary Reviewer	Deepa Rao OCP DCEP	Sections: IRT Sections 5, 6, 8 and 14	Based on my assessment of the application: ☒ <u>No</u> deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Deepa Rao Digitally signed by Deepa Rao Date: 12/13/2024 2:46 PM EST GUID: 20241213194650				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
CMC (OPQ/ONDP) Discipline Primary Reviewer	George Ward OPQAI DPQAI	Sections: 9, 23	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	
Signature: George Ward Digitally signed by George Ward Date: 12/13/2024 2:55 PM EST GUID: 20241213195534				

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Pharm-tox/Non-clinical Discipline Primary Reviewer	Mekonnen Lemma Dechassa OCHEN DPTCHEN	Sections: 5, 7, 8, 13	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

NDA 218808 and NDA 218820
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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Mekonnen Lemma Dechassa		Digitally signed by Mekonnen Lemma Dechassa Date: 12/13/2024 3:00 PM EST GUID: 2024121320013		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Secondary Reviewer	Li Li OCP DCEP	Sections: Sections 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	This NDA is approvable from a clinical pharmacology perspective.
Signature: Li Li		Digitally signed by Li Li Date: 12/13/2024 3:32 PM EST GUID: 20241213203251		

Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Clinical Pharmacology Discipline Associate Director	Jayabharathi Vaidyanathan OCP DCEP	Sections: 5.2, 6.1, 8.1, 8.2, 14	Based on my assessment of the application: ☒ No deficiencies preclude approval. ☐ Deficiencies preclude approval. ☐ Not applicable.	

NDA 218808 and NDA 218820
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Discipline and Role	Reviewer Name, Office/Center, and Division	Sections Authored in Full or in Part	Recommendation to Signatory	Comments on Recommendation to Signatory
Signature: Jayabharathi Vaidyanathan		Digitally signed by Jayabharathi Vaidyanathan Date: 12/13/2024 3:39 PM EST GUID: 20241213203940		

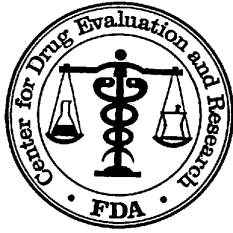
This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

OLIVIA J EASLEY
12/13/2024 02:04:29 PM

THERESA E KEHOE
12/13/2024 02:12:00 PM

HYLTON V JOFFE
12/13/2024 04:05:18 PM



U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Office of Translational Sciences

Office of Biostatistics

Statistical Review and Evaluation

CARCINOGENICITY STUDY

IND/NDA Number: NDA218808

Drug Name: Crinecerfont (CRENESSITY)

Indication:

(b) (4)

Applicant:

Neurocrine Biosciences, Inc.
12780 El Camino Real
San Diego, CA 92130

Test Facility: (b) (4)

(b) (4)

Documents Reviewed:

Study reports (Rat Study No. 882-098 and No. 882-097) on April 29, 2024 via NDA218808/0001 and electronic data submitted on June 06, 2024 via NDA218808/0003

Biometrics Division:	Division of Biometrics -6
Statistical Reviewer:	Zhuang Miao, Ph.D.
Concurring Reviewer:	Rahman, Atiar Mohammad, Ph.D.
Reviewing Pharmacologist:	LemmaDechassa, Mekonnen, Ph.D.
Keywords:	Carcinogenicity, Dose response

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1. Summary

In this submission the sponsor included reports of two animal carcinogenicity studies, one in CD[CrI:CD(SD)] rats and one in CByB6F1-Tg(HRAS)2Jic mice. These studies were intended to assess the carcinogenic potential of Crinecerfont, when administered via oral gavage at appropriate drug levels for 100 weeks in rats and 26 weeks in mice.

Rat Study:

Survival data analyses:

1. For male rats, the survival analyses didn't show any statistically significant dose response relationship in mortality across the water control group and treated groups. However, p-value of the likelihood ratio test is $0.0152 < 0.05$ but the p-value of log-rank test is $0.0675 > 0.05$. The pairwise comparisons did not show any statistically significant differences in mortality between the water control group and treated groups.
2. For male rats, the survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle control group and treated groups. However, p-value of the likelihood ratio test is $0.0120 < 0.05$ but the p-value of log-rank test is $0.0563 > 0.05$. The pairwise comparisons showed statistically significant differences in mortality between the vehicle control group and the high dose group. The p-value of the likelihood ratio test is $0.0428 < 0.05$ and the p-value of log-rank test is $0.0393 < 0.05$.
3. For female rats, the survival analyses didn't show any statistically significant dose response relationship in mortality across the water control group and treated groups or across the vehicle control group and the treated groups. The pairwise comparisons did not show any statistically significant differences in mortality between the water control group and treated groups or between the vehicle control group and the treated groups.

Tumor data analysis:

1. For female rats, the tumor data analysis showed statistically significant positive dose response relationships across the water control and the treated groups in the incidences of adenoma, follicular cell, thyroid gland (P-value < 0.001), carcinoma follicular cell, thyroid gland (P-value $= 0.0032 < 0.025$), and combined adenoma+carcinoma, follicular cell, thyroid gland (P-value < 0.001). The pairwise comparisons between the water control and the high dose group showed

- statistically significant increases in the incidences of adenoma, follicular cell, thyroid gland (P-value=0.0041<0.05), carcinoma follicular cell, thyroid gland (P-value=0.0332<0.05), and combined adenoma+carcinoma, follicular cell, thyroid gland (P-value<0.001).
2. For female rats, the tumor data analysis showed statistically significant positive dose response relationships across the vehicle control and the treated groups in the incidences of adenoma, follicular cell, thyroid gland (P-value<0.001), carcinoma follicular cell, thyroid gland (P-value=0.0032<0.025), combined adenoma+carcinoma, follicular cell, thyroid gland (P-value<0.001) and schwannoma, uterus with cervix (P-value=0.0205<0.025). The pairwise comparisons between the vehicle control and the low dose group showed statistically significant increases in the incidences of pheochromocytoma, adrenal glands (P-value=0.0065<0.05). The pairwise comparisons between the vehicle control and the high dose group showed statistically significant increases in the incidences of pheochromocytoma, adrenal glands (P-value=0.015<0.05), carcinoma follicular cell, thyroid gland (P-value=0.0312<0.05), and combined adenoma+carcinoma, follicular cell, thyroid gland (P-value=0.0027<0.01).

Mouse Study:

Survival data analyses:

1. The survival analyses didn't show any statistically significant dose response relationship in mortality across the water control group and treated groups for either males or females. The pairwise comparisons did not show any statistically significant differences in mortality between the water control group and any of the treated groups in either males or females.
2. The survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle control group and treated groups for either males or females. The pairwise comparisons did not show any statistically significant differences in mortality between the vehicle control group and any of the treated groups in either males or females.

Tumor data analysis:

1. For male mice, the pairwise comparisons between the water control and the

- positive control showed statistically significant increases in the incidences of papilloma, skin ($p\text{-value}=0.0027<0.05$) and papilloma, stomach ($p\text{-value}<0.001$).
2. For male mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in the incidences of papilloma, skin ($p\text{-value}<0.001$) and papilloma, stomach ($p\text{-value}<0.001$).
 3. For female mice, the pairwise comparisons between the water control and the positive control showed statistically significant increases in the incidences of papilloma, skin ($p\text{-value}<0.001$) and papilloma, stomach ($p\text{-value}<0.001$).
 4. For female mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in the incidences of papilloma, skin ($p\text{-value}<0.001$) and papilloma, stomach ($p\text{-value}<0.001$).

2. Background

In this submission the sponsor included reports of two animal carcinogenicity studies, one in CD[CrI:CD(SD)] rats and one in CByB6F1-Tg(HRAS)2Jic mice. These studies were intended to assess the carcinogenic potential of Crinacerfont, when administered via administered by oral gavage at appropriate drug levels for 100 weeks in rats and 26 weeks in mice.

In this review the phrase "dose response relationship" refers to the linear component of the effect of treatment, and not necessarily to a strictly increasing or decreasing mortality or tumor incidence rate as the dose increases.

3. Rat Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were three treated groups, one water group and one vehicle control group. Three hundred and fifty rats of each sex were randomly assigned to the five groups in equal size of 70 rats per group. The dose levels for treated groups were 5, 15 and 100 mg/kg/day. The rats in the water control group received the De-ionized water. The study for the rats was designed to continue for up to 100 weeks.

Table 1: Study Design in Rat Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Water	70	70
2	0	Vehicle	70	70
3	5	Low	70	70
4	15	Mid	70	70
5	100	High	70	70

3.1. Sponsor's analyses

3.1.1. Survival analysis

Intercurrent mortality data was analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups was conducted using a log-rank test (Allison, PD, 1995). If this overall test was significant ($p < 0.05$) and there were more than two groups, then a follow up analysis was done where each treatment group was compared to the control group using a log-rank test.

Results of all pair-wise comparisons were reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's findings: Sponsor's analysis showed the numbers (percents) of survival were 20 (29%), 21 (30%), 20 (29%), 18 (26%), and 15 (21%) in water, vehicle, and low, mid, high dose groups, respectively in males and 20 (29%), 22 (31%), 17 (24%), 23 (33%), and 23 (33%) in water, vehicle, and low, mid, high dose groups, respectively in females.

No NBI-74788-related unscheduled deaths or euthanasias occurred in either sex, and no statistically significant survival differences were noted.

3.1.2. Tumor data analysis

Tumor incidence data was analyzed using both survival adjusted and unadjusted tests. The unadjusted tests were based on the incidence and number of sites examined for each tumor type. The Cochran-Armitage test (Agresti, A. 1999) was for trend test and Fisher's exact test (Zar JH, 1999) was used to compare each treatment group with the control group. Trend test was applied for all control and treatment groups that were arranged in a strictly increasing dose level. The survival adjusted test was conducted according to the prevalence/mortality methods described by Peto et al (Peto et al, 1980). The Poly-3 method (Bieler and Williams, 1993) (Bailer and Portier, 1988) was used to assess prevalence of tumors. The survival-adjusted rates based on the risk weights was displayed. The tests of significance included both an overall trend and pair-wise comparisons of each treatment group with the control. All p-values were reported using upper-tailed tests, unless otherwise indicated.

Sponsor's findings: Test article-related neoplastic microscopic findings were limited to an increased incidence of benign and malignant thyroid follicular cell tumors (adenomas and carcinomas) in females at 100 mg/kg/day.

3.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing

pharmacologist, this reviewer independently performed survival and tumor data analyses.

3.2.1. Survival analysis

The survival distributions of animals in four groups were estimated by the Kaplan-Meier product limit method. The dose response relationship and homogeneity of survival distributions were tested for the water control, vehicle control, low, medium and high dose groups using the Likelihood Ratio test and the Log-Rank test. The intercurrent mortality data are given in Tables 11 and 12 in the appendix for males and females, respectively. The Kaplan-Meier curves for survival rate are given in Figures 1 and 2 in the appendix for males and females, respectively. Results of the tests for dose response relationship and homogeneity of survivals, are given in Tables 13 to 16 in the appendix for males and females, respectively.

Reviewer's findings: This reviewer's analysis showed the numbers (percents) of survival were 20 (29%), 21 (30%), 20 (29%), 18 (26%), and 15 (21%) in water, vehicle, and low, mid, high dose groups, respectively in males and 20 (29%), 22 (31%), 17 (24%), 23 (33%), and 23 (33%) in water, vehicle, and low, mid, high dose groups, respectively in females.

For male rats, the survival analyses didn't show any statistically significant dose response relationship in mortality across the water control group and treated groups. However, p-value of the likelihood ratio test is $0.0152 < 0.05$ but the p-value of log-rank test is $0.0675 > 0.05$. The pairwise comparisons did not show any statistically significant differences in mortality between the water control group and treated groups.

For male rats, the survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle control group and treated groups. However, p-value of the likelihood ratio test is $0.0120 < 0.05$ and the p-value of log-rank test is $0.0563 > 0.05$. The pairwise comparisons showed statistically significant differences in mortality between the vehicle control group and the high dose group. The p-value of the likelihood ratio test is $0.0428 < 0.05$ and the p-value of log-rank test is $0.0393 < 0.05$.

For female rats, the survival analyses didn't show any statistically significant dose response relationship in mortality across the water control group and treated groups or across the vehicle control group and the treated groups. The pairwise comparisons did not show any statistically significant differences in mortality between the water control group and treated groups or between the vehicle control group and the treated groups.

3.2.2. Tumor data analysis

The tumor data were analyzed for the positive dose response relationships and the positive pairwise comparison increases between each of the treated groups with control group. Both the dose response relationship tests and pairwise comparisons were performed using the Poly-K method described in the paper of Bailer and Portier (1988) and Bieler and Williams (1993). In this method an animal that lives the full study period ($w_{\max}$) or dies before the terminal sacrifice but develops the tumor type being tested gets a score of $s_h = 1$. An animal that dies at week w_h without a tumor before the end of the study gets a score of $s_h = \left(\frac{w_h}{w_{\max}} \right)^k$ < 1 . The adjusted group size is defined as $\sum s_h$. As an interpretation, an animal with score $s_h = 1$ can be considered as a whole animal while an animal with score $s_h < 1$ can be considered as a partial animal. The adjusted group size $\sum s_h$ is equal to N (the original group size) if all animals live up to the end of the study or if each animal that dies before the terminal sacrifice develops at least one tumor, otherwise the adjusted group size is less than N. These adjusted group sizes were then used for the dose response relationship (or the pairwise) tests using the Cochran-Armitage test. One critical point for Poly-k test is the choice of the appropriate value of k, which depends on the tumor incidence pattern with the increased dose. For long term 104 week standard rat and mouse studies, a value of k=3 is suggested in the literature. Hence, this reviewer used k=3 for the analysis of this data. For the calculation of p-values the exact permutation method was used. The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons are listed in Tables 17 to 20 in the appendix for male and female rats, respectively.

Adjustment for multiple testing: For the chronic study in rats, the adjustment of multiple testing of the dose response relationship for a submission with one chronic rat study and one transgenic mouse study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels $\alpha = 0.005$ for common tumors and $\alpha = 0.025$ for rare tumors for the chronic rat study. For pairwise comparisons for the chronic rat study in the above type of submission with one chronic rat study and one transgenic mouse study, the same guidance document suggests the use of test levels $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors for the chronic rat study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: The tumor types in Tables 2 to 5 below showed p-values less than or equal to 0.05 in the tests for pairwise comparisons between vehicle control and treated groups for males.

Based on the criteria of adjustment for multiple testing discussed in the data analysis section, we make the following statistical conclusions:

1. For female rats, the tumor data analysis showed statistically significant positive dose response relationships across the water control and the treated groups in incidences of adenoma, follicular cell, thyroid gland ($P\text{-value} < 0.001$), carcinoma follicular cell, thyroid gland ($P\text{-value} = 0.0032 < 0.025$), and combined adenoma+carcinoma, follicular cell, thyroid gland ($P\text{-value} < 0.001$). The pairwise comparisons between the water control and the high dose group showed statistically significant increases in the incidences of adenoma, follicular cell, thyroid gland ($P\text{-value} = 0.0041 < 0.05$), carcinoma follicular cell, thyroid gland ($P\text{-value} = 0.0332 < 0.05$), and combined adenoma+carcinoma, follicular cell, thyroid gland ($P\text{-value} < 0.001$).
2. For female rats, the tumor data analysis showed a statistically significant positive dose response relationships across the vehicle control and the treated groups in the incidences of adenoma, follicular cell, thyroid gland ($P\text{-value} < 0.001$), carcinoma follicular cell, thyroid gland ($P\text{-value} = 0.0032 < 0.025$), combined adenoma+carcinoma, follicular cell, thyroid gland ($P\text{-value} < 0.001$) and schwannoma, uterus with cervix ($P\text{-value} = 0.0205 < 0.025$). The pairwise comparisons between the vehicle control and the low dose group showed statistically significant increases in incidences of pheochromocytoma, adrenal glands ($P\text{-value} = 0.0065 < 0.05$). The pairwise comparisons between the vehicle control and the high dose group showed statistically significant increases in

incidences of pheochromocytoma, adrenal glands (P-value=0.015<0.05), carcinoma follicular cell, thyroid gland (P-value=0.0312<0.05), and combined adenoma+carcinoma, follicular cell, thyroid gland (P-value=0.0027<0.01).

Table 2: Tumor Types with P-Values ≤ 0.05 for Comparisons between Water Control and Treated Groups -Male Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Water vs. Low	15 mg/kg/day Med (N=70) P-value - Water vs. Med	100 mg/kg/day High (N=70) P-value - Water vs. High
MULTICENTRIC NEOPL	LEUKEMIA, GRANULOCYTIC, MALIGNANT	0/70 (30) 0.0435	0/70 (34) NC	0/70 (29) NC	2/70 (25) 0.2020
THYMUS	THYMOMA, BENIGN	0/70 (30) 0.0435	0/70 (34) NC	0/70 (29) NC	2/70 (25) 0.2020
THYROID GLAND	ADENOMA, FOLLICULAR CELL, BENIGN	1/70 (31) 0.0056	0/70 (34) 1.0000	3/70 (30) 0.2937	5/70 (27) 0.0691
Thymus	C_Thymoma Benign+Malignant	0/70 (30) 0.0413	0/70 (34) NC	1/70 (30) 0.5000	2/70 (25) 0.2020
Thyroid Gland	C_Follicular cell adenoma+carcinoma	2/70 (32) 0.0096	1/70 (34) 0.8916	3/70 (30) 0.4687	6/70 (27) 0.0800
& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.					

Table 3: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle Control and Treated Groups -Male Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	100 mg/kg/day High (N=70) P-value - Vehicle vs. High
THYMUS	THYMOMA, BENIGN	0/70 (31) 0.0427	0/70 (34) NC	0/70 (29) NC	2/70 (25) 0.1948
THYROID GLAND	ADENOMA, FOLLICULAR CELL, BENIGN	3/70 (32) 0.0326	0/70 (34) 1.0000	3/70 (30) 0.6325	5/70 (27) 0.2606
Thymus	C_Thymoma Benign+Malignant	0/70 (31) 0.0402	0/70 (34) NC	1/70 (30) 0.4918	2/70 (25) 0.1948
Thyroid Gland	C_Follicular cell adenoma+carcinoma	3/70 (32) 0.0204	1/70 (34) 0.9501	3/70 (30) 0.6325	6/70 (27) 0.1579
& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.					

Table 4: Tumor Types with P-Values ≤ 0.05 for Comparisons between Water Control and Treated Groups -Female Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Water vs. Low	15 mg/kg/day Med (N=70) P-value - Water vs. Med	100 mg/kg/day High (N=70) P-value - Water vs. High
THYROID GLAND	ADENOMA, FOLLICULAR CELL, BENIGN	0/70 (40) <0.001	1/70 (41) 0.5062	1/70 (41) 0.5062	8/70 (44) 0.0041
	CARCINOMA, FOLLICULAR CELL, MALIGNANT	0/70 (40) 0.0032	1/70 (42) 0.5122	0/70 (41) NC	5/70 (43) 0.0332
Thyroid Gland	C_Follicular cell adenoma+carcinoma	0/70 (40) <0.001	2/70 (42) 0.2593	1/70 (41) 0.5062	13/70 (45) <0.001
& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.					

Table 5: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle

Control and Treated Groups -Female Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	100 mg/kg/day High (N=70) P-value - Vehicle vs. High
ADRENAL GLANDS	PHEOCHROMOCYTOMA, BENIGN	0/70 (41) 0.0992	7/70 (42) 0.0065	2/70 (41) 0.2469	6/70 (43) 0.0150
THYROID GLAND	ADENOMA, FOLLICULAR CELL, BENIGN	2/70 (42) 0.0021	1/70 (41) 0.8751	1/70 (41) 0.8751	8/70 (44) 0.0522
	CARCINOMA, FOLLICULAR CELL, MALIGNANT	0/70 (41) 0.0031	1/70 (42) 0.5060	0/70 (41) NC	5/70 (43) 0.0312
Thyroid Gland	C_Follicular cell adenoma+carcinoma	2/70 (42) <0.001	2/70 (42) 0.6921	1/70 (41) 0.8751	13/70 (45) 0.0027
UTERUS WITH CERVIX	SCHWANNOMA, MALIGNANT	0/70 (41) 0.0205	0/70 (41) NC	1/70 (42) 0.5060	3/70 (43) 0.1295
& X/ZZ (YY): X=number of tumor bearing animals; YY=mortality weighted total number of animals; ZZ=unweighted total number of animals observed; NC = Not calculable.					

4. Mouse Study

Two separate experiments were conducted, one in males and one in females. In each of these two experiments there were four treated groups, one water group, one vehicle control group and one positive control group. Two hundred and fifty mice of each sex were randomly assigned to the treated and control groups. There are 25 mice in water control group. There are 35 mice in each of the vehicle control group and treated groups. The dose levels for treated groups were 15, 50, 500 and 1500 mg/kg/day for males and females. There were ten mice in positive control group for each sex. Animals in positive control group were administered once via intraperitoneal (IP) injection once on Day 1. The positive control article was N-Nitroso-N-methylurea (NMU).

Table 6: Study Design in Mouse Study

Protocol Group No.	Dose Levels (mg/kg/day)	Identification	Number of Animals Enrolled	
			Males	Females
1	0	Water	25	25
2	0	Vehicle	35	35
3	15	Low	35	35
4	50	Mid	35	35
5	500	High	35	35
6	1500	High 2	35	35
7	75	Positive	10	10

4.1. Sponsor's analyses

4.1.1. Survival analysis

Intercurrent mortality data were analyzed using the Kaplan-Meier product-limit method. An overall test comparing all groups was conducted using a log-rank test (Allison, 1995). If this overall test was significant ($p < 0.05$), then a follow up analysis was done where each treatment group was compared to the control group using a log-rank test.

Results of all pair-wise comparisons were reported at the 0.05 and 0.01 significance levels. All endpoints were analyzed using two-tailed tests.

Sponsor's findings: The sponsor's analysis showed that the numbers (percents) of survival were 23 (92%), 32 (91%), 32 (91%), 33 (94%), 32 (91%), 33 (94%) and 8 (80%) in male mice, and 25 (100%), 31 (89%), 32 (91%), 32 (91%), 35 (100%), 35 (100%) and 9 (90%) in female

mice in water control, vehicle control, low, medium, high and high 2 dose groups, respectively.

The sponsor concluded that, no test article-related mortality occurred and evaluations of survival revealed no statistically significant differences.

4.1.2. Tumor data analysis

Tumor incidence data were analyzed using both survival adjusted and unadjusted tests. The unadjusted tests were based on the incidence and number of sites examined for each tumor type. The Cochran-Armitage test (Agresti, 2002) was for trend and Fisher's exact test (Zar, 1999) was used to compare each treatment group with the control group. Trend test was applied for all control and treatment groups that could be arranged in a strictly increasing dose level. The survival adjusted test was conducted according to the prevalence/mortality methods described by Peto et al (Peto R, Pike MC, Day NE et al, 1980).

The Poly-3 method (Bailer and Portier, 1988) (Bieler and Williams, 1993) was used to assess prevalence of tumors. The survival-adjusted rates based on the risk weights were displayed. The tests of significance included both an overall trend and pair-wise comparisons of each treatment group with the control. All p-values were reported using upper-tailed tests, unless otherwise indicated.

Sponsor's findings: The sponsor concluded that the occurrence of none of the observed tumors in the NBI-74788-treated groups were statistically significant when compared to the control groups.

4.2. Reviewer's analyses

To verify sponsor's analyses and to perform additional analyses suggested by the reviewing pharmacologist, this reviewer independently performed survival and tumor data analyses.

4.2.1. Survival analysis

The survival distributions of three treated groups, one vehical control group, and one positive

control group were estimated using the Kaplan-Meier product limit method. The dose response relationship in survival was tested using the likelihood ratio test and the homogeneity of survival distributions was tested using the log-rank test. The Kaplan-Meier curves for survival rates are given in Figures 3 and 4 in the appendix for male and female mice, respectively. The intercurrent mortality data are given in Tables 21 and 22 in the appendix for male and female mice, respectively. Results of the tests for dose response relationship and homogeneity of survivals among the water control, vehicle control, positive control and the treated groups are given in Tables 23 to 26 in the appendix for male and female mice, respectively.

Reviewer's findings: This reviewer's analysis showed that the numbers (percents) of survival were 23 (92%), 32 (91%), 32 (91%), 33 (94%), 32 (91%), 33 (94%) and 8 (80%) in male mice, and 25 (100%), 31 (89%), 32 (91%), 32 (91%), 35 (100%), 35 (100%) and 9 (90%) in female mice in water control, vehicle control, low, medium, high and high 2 dose groups, respectively.

The survival analyses didn't show any statistically significant dose response relationship in mortality across the water control group and treated groups in either male or female. The pairwise comparisons did not show statistically significant difference in mortality between the water control group and any of the treated groups in either male or female mice.

The survival analyses didn't show any statistically significant dose response relationship in mortality across the vehicle control group and treated groups in either male or female. The pairwise comparisons did not show statistically significant difference in mortality between the vehicle control group and any of the treated groups in either male or female mice.

4.2.2. Tumor data analysis

The reviewer used the same tumor data analysis methods for the mouse study as was used for rat study.

The tumor rates and the p-values for the positive dose response relationship tests and pairwise comparisons between water/vehicle control and the treated groups, and between water/vehicle and positive control are listed in Tables 27 to 34 in the appendix for male and

female mice, respectively.

Adjustment for multiple testing: For the adjustment of multiple testing of the dose response relationship for a submission with one 2 year chronic rat study and one 26 week chronic mouse study, the more recently revised draft (January, 2013) FDA guidance for the carcinogenicity studies suggests the use of test levels $\alpha = 0.005$ for common tumors and $\alpha = 0.025$ for rare tumors for the chronic mouse study. For pairwise comparisons of submission with one 2 year chronic rat study and one 26 week chronic mouse study, the same guidance document suggests the use of test levels $\alpha = 0.01$ for common tumors and $\alpha = 0.05$ for rare tumors for the chronic mouse study.

It should be noted that the FDA guidance for multiple testing for dose response relationship is based on a publication by Lin and Rahman (1998). In this work the authors investigated the use of this rule for Peto analysis. However, in a later work Rahman and Lin (2008) showed that this rule for multiple testing for dose response relationship is also suitable for Poly-K tests.

Reviewer's findings: The tumor types in Tables 7 to 10 below showed p-values less than or equal to 0.05 in the tests between vehicle control and treated groups for males.

Based on the criteria of adjustment for multiple testing discussed in the mouse data analysis section, we make the following statistical conclusions:

1. For male mice, the pairwise comparisons between the water control and the positive control showed statistically significant increases in incidence of papilloma, skin (p-value=0.0027<0.05) and papilloma, stomach (p-value<0.001).
2. For male mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of papilloma, skin (p-value<0.001) and papilloma, stomach (p-value<0.001).
3. For female mice, the pairwise comparisons between the water control and the positive control showed statistically significant increases in incidence of papilloma, skin (p-value<0.001) and papilloma, stomach (p-value<0.001).
4. For female mice, the pairwise comparisons between the vehicle control and the positive control showed statistically significant increases in incidence of

papilloma, skin (p-value<0.001) and papilloma, stomach (p-value<0.001).

Table 7: Tumor Types with P-Values ≤ 0.05 for Comparisons between Water Control and Positive Control -Male Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	75 mg/kg/day Positive (N=10) P-value - Water vs. Positive
SKIN	PAPILLOMA, BENIGN	0/25 (25)	4/10 (9) 0.0027
STOMACH	PAPILLOMA, BENIGN	0/25 (25)	8/10 (9) <0.001

Table 8: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle Control and Positive Control -Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=35)	75 mg/kg/day Positive (N=10) P-value - Vehicle vs. Positive
SKIN	PAPILLOMA, BENIGN	0/35 (35)	4/10 (9) <0.001
STOMACH	PAPILLOMA, BENIGN	1/35 (35)	8/10 (9) <0.001

Table 9: Tumor Types with P-Values ≤ 0.05 for Comparisons between Water Control and Positive Control -Female Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	75 mg/kg/day Positive (N=10) P-value - Water vs. Positive
SKIN	PAPILLOMA, BENIGN	1/25 (25)	6/10 (10) <0.001
STOMACH	PAPILLOMA, BENIGN	0/25 (25)	10/10 (10) <0.001

Table 10: Tumor Types with P-Values ≤ 0.05 for Comparisons between Vehicle

Control and Positive Control -Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=35)	75 mg/kg/day Positive (N=10) P-value - Vehicle vs. Positive
SKIN	PAPILLOMA, BENIGN	0/35 (33)	6/10 (10) <0.001
STOMACH	PAPILLOMA, BENIGN	1/35 (33)	10/10 (10) <0.001

Zhuang Miao,

Ph.D.

Mathematical

Statistician

Concur:

Rahman, Atiar Mohammad, Ph.D.

Mathematical Statistician, Acting Team Leader, Biometrics-6

cc:

Yi Tsong, Ph.D.

5. Appendix

Table 11: Intercurrent Mortality Rate -Male Rats

	0 mg/kg/day Water (N=70)		0 mg/kg/day Vehicle (N=70)		5 mg/kg/day (N=70)		15 mg/kg/day (N=70)		100 mg/kg/day (N=70)	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	11	15.71	9	12.86	5	7.14	13	18.57	13	18.57
53 - 78	25	51.43	26	50.00	22	38.57	24	52.86	29	60.00
79 - 91	12	68.57	13	68.57	20	67.14	11	68.57	13	78.57
92 - 104	2	71.43	1	70.00	3	71.43	4	74.29	.	.
Ter. Sac.	20	28.57	21	30.00	20	28.57	18	25.71	15	21.43

Cum. %: Cumulative percentage except for Ter. Sac.

Table 12: Intercurrent Mortality Rate -Female Rats

	0 mg/kg/day Water (N=70)		0 mg/kg/day Vehicle (N=70)		5 mg/kg/day (N=70)		15 mg/kg/day (N=70)		100 mg/kg/day (N=70)	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 52	5	7.14	4	5.71	2	2.86	4	5.71	4	5.71
53 - 78	21	37.14	20	34.29	22	34.29	18	31.43	20	34.29
79 - 91	16	60.00	18	60.00	18	60.00	18	57.14	13	52.86
92 - 104	8	71.43	6	68.57	11	75.71	7	67.14	10	67.14
Ter. Sac.	20	28.57	22	31.43	17	24.29	23	32.86	23	32.86

Cum. %: Cumulative percentage except for Ter. Sac.

Table 13: Intercurrent Mortality Comparison between Treated Groups and Water Control - Male Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.0152	0.5686	0.6642	0.0624
Homogeneity	Log-Rank	0.0675	0.5626	0.6602	0.0584

Table 14: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control-Male Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.0120	0.6600	0.5594	0.0428
Homogeneity	Log-Rank	0.0563	0.6543	0.5546	0.0393

Table 15: Intercurrent Mortality Comparison between Treated Groups and Water Control - Female Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.4788	0.8713	0.6200	0.5491
Homogeneity	Log-Rank	0.8292	0.8695	0.6159	0.5431

Table 16: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control - Female Rats

Test	Statistic	P_Value Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Medium	P_Value Vehicle vs. High
Dose-Response	Likelihood Ratio	0.6126	0.5648	0.9382	0.8171
Homogeneity	Log-Rank	0.8608	0.5591	0.9374	0.8148

Table 17: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Water Control and the Treated Groups-Male Rats

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Water vs. Low	15 mg/kg/day Med (N=70) P-value - Water vs. Med	100 mg/kg/day High (N=70) P-value - Water vs. High
ADRENAL GLANDS	ADENOMA, CORTICAL, BENIGN	3/70 (32) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
	CARCINOMA, CORTICAL, MALIGNANT	1/70 (31) 0.6987	0/70 (34) 1.0000	1/70 (29) 0.7373	0/70 (24) 1.0000
	PHEOCHROMOCYTOMA, BENIGN	6/70 (33) 0.6095	4/70 (35) 0.8705	2/70 (30) 0.9633	3/70 (25) 0.8434
BONE MARROW, FEMUR	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (30) 0.7436	1/70 (34) 0.5312	0/70 (29) NC	0/70 (24) NC
BONE MARROW, STERN	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (30) 0.7436	1/70 (34) 0.5312	0/70 (29) NC	0/70 (24) NC
BONE, FEMUR	OSTEOSARCOMA, MALIGNANT	0/70 (30) 0.7436	1/70 (34) 0.5312	0/70 (29) NC	0/70 (24) NC
BRAIN	CARCINOMA, NEUROEPITHELIAL, MALIGNANT	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	GLIOMA, MALIGNANT	1/70 (31) 0.9326	1/70 (34) 0.7764	0/70 (29) 1.0000	0/70 (24) 1.0000
	GRANULAR CELL TUMOR, BENIGN	0/70 (30) 0.5776	1/70 (34) 0.5312	1/70 (30) 0.5000	0/70 (24) NC
	GRANULAR CELL TUMOR, MALIGNANT	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	OLIGODENDROGLIOMA, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
HARDERIAN GLANDS	CARCINOMA, NEUROEPITHELIAL, MALIGNANT	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
HEART	SCHWANNOMA, ENDOCARDIAL, MALIGNANT	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
KIDNEYS	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
	LIPOMA, BENIGN	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
LIVER	ADENOMA, HEPATOCELLULAR, BENIGN	0/70 (30) 0.4530	0/70 (34) NC	1/70 (29) 0.4915	0/70 (24) NC
	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Water vs. Low	15 mg/kg/day Med (N=70) P-value - Water vs. Med	100 mg/kg/day High (N=70) P-value - Water vs. High
	CARCINOMA, HEPATOCELLULAR, MALIGNANT	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (30) 0.7436	1/70 (34) 0.5312	0/70 (29) NC	0/70 (24) NC
LUNG	ADENOMA, BRONCHIOLAR ALVEOLAR, BENIGN	0/70 (30) 0.7436	1/70 (34) 0.5312	0/70 (29) NC	0/70 (24) NC
	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
LYMPH NODE, MEDIAS	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
Liver	C_Hepatocellular adenoma+carcinoma	1/70 (31) 0.6987	0/70 (34) 1.0000	1/70 (29) 0.7373	0/70 (24) 1.0000
MAMMARY GLAND	ADENOCARCINOMA, MALIGNANT	0/70 (30) 0.7436	1/70 (34) 0.5312	0/70 (29) NC	0/70 (24) NC
	ADENOMA, BENIGN	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	FIBROADENOMA, BENIGN	5/70 (34) 0.7961	1/70 (34) 0.9877	0/70 (29) 1.0000	1/70 (24) 0.9668
MEDIASTINUM/PLE URA	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
MESENTERY/PERIT ONE	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
	LIPOMA, BENIGN	0/70 (30) 0.7436	1/70 (34) 0.5312	0/70 (29) NC	0/70 (24) NC
	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (30) 0.7436	1/70 (34) 0.5312	0/70 (29) NC	0/70 (24) NC
MULTICENTRIC NEOPL	HEMANGIOMA, BENIGN	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
	HEMANGIOSARCOMA, MALIGNANT	0/70 (30) 0.7436	1/70 (34) 0.5312	0/70 (29) NC	0/70 (24) NC
	LEUKEMIA, GRANULOCYTIC, MALIGNANT	0/70 (30) 0.0435	0/70 (34) NC	0/70 (29) NC	2/70 (25) 0.2020
	LYMPHOMA, MALIGNANT	0/70 (30) 0.3749	2/70 (35) 0.2861	0/70 (29) NC	1/70 (25) 0.4545
	SARCOMA, HISTIOCYTIC, MALIGNANT	0/70 (30) 0.4576	0/70 (34) NC	1/70 (30) 0.5000	0/70 (24) NC
NOSE	ADENOMA, BENIGN	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	CARCINOMA, NEUROEPITHELIAL, MALIGNANT	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	CARCINOMA, SQUAMOUS CELL, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Water vs. Low	15 mg/kg/day Med (N=70) P-value - Water vs. Med	100 mg/kg/day High (N=70) P-value - Water vs. High
PANCREAS	ADENOMA, ACINAR CELL, BENIGN	2/70 (31) 0.5898	5/70 (36) 0.2806	3/70 (30) 0.4841	2/70 (25) 0.6084
	ADENOMA, ISLET CELL, BENIGN	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
	CARCINOMA, ISLET CELL, MALIGNANT	4/70 (32) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (30) 0.7436	1/70 (34) 0.5312	0/70 (29) NC	0/70 (24) NC
PARATHYROID GLANDS	ADENOMA, BENIGN	1/70 (31) 0.7242	1/70 (34) 0.7764	2/70 (30) 0.4875	0/70 (24) 1.0000
PITUITARY GLAND	ADENOMA, PARS DISTALIS, BENIGN	33/70 (47) 0.8236	40/70 (53) 0.3569	40/70 (50) 0.1892	26/70 (39) 0.7215
	ADENOMA, PARS INTERMEDIA, BENIGN	0/70 (30) 0.4576	0/70 (34) NC	1/70 (30) 0.5000	0/70 (24) NC
	CARCINOMA, PARS DISTALIS, MALIGNANT	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
PROSTATE GLAND	ADENOMA, BENIGN	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
Pancreas	C_Acinar cell+Islet cell adenoma	3/70 (31) 0.6794	5/70 (36) 0.4430	3/70 (30) 0.6484	2/70 (25) 0.7496
SEMINAL VESICLES	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
SKELETAL MUSCLE	FIBROSARCOMA, MALIGNANT	0/70 (30) 0.4530	0/70 (34) NC	1/70 (29) 0.4915	0/70 (24) NC
SKIN	KERATOACANTHOMA, BENIGN	2/70 (31) 0.9832	1/70 (34) 0.8971	0/70 (29) 1.0000	0/70 (24) 1.0000
	PAPILLOMA, FIBROUS, BENIGN	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	PAPILLOMA, SQUAMOUS CELL, BENIGN	0/70 (30) 0.6750	2/70 (35) 0.2861	1/70 (29) 0.4915	0/70 (24) NC
SKIN, SUBCUTIS	FIBROMA, BENIGN	2/70 (32) 0.5808	5/70 (36) 0.2658	2/70 (30) 0.6688	2/70 (25) 0.5950
	FIBROSARCOMA, MALIGNANT	2/70 (32) 0.2705	1/70 (34) 0.8916	0/70 (29) 1.0000	2/70 (25) 0.5950
	LIPOMA, BENIGN	0/70 (30) 0.1432	0/70 (34) NC	1/70 (29) 0.4915	1/70 (24) 0.4444
	LIPOSARCOMA, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Water vs. Low	15 mg/kg/day Med (N=70) P-value - Water vs. Med	100 mg/kg/day High (N=70) P-value - Water vs. High
	SARCOMA, UNDIFFERENTIATED, MALIGNANT	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	SCHWANNOMA, MALIGNANT	0/70 (30) 0.4530	0/70 (34) NC	1/70 (29) 0.4915	0/70 (24) NC
SMALL INTESTINE, D	ADENOCARCINOMA, MALIGNANT	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
SMALL INTESTINE, J	ADENOCARCINOMA, MALIGNANT	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
SPLEEN	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (30) 0.7436	1/70 (34) 0.5312	0/70 (29) NC	0/70 (24) NC
	SARCOMA, UNDIFFERENTIATED, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
STOMACH	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (30) 0.2051	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4444
Skin	C_Keratoacanthoma+Papilloma	3/70 (32) 0.9955	1/70 (34) 0.9501	0/70 (29) 1.0000	0/70 (24) 1.0000
TESTES	ADENOMA, LEYDIG CELL, BENIGN	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	ADENOMA, RETE TESTIS, BENIGN	0/70 (30) 0.7436	1/70 (34) 0.5312	0/70 (29) NC	0/70 (24) NC
THYMUS	THYMOMA, BENIGN	0/70 (30) 0.0435	0/70 (34) NC	0/70 (29) NC	2/70 (25) 0.2020
	THYMOMA, MALIGNANT	0/70 (30) 0.4576	0/70 (34) NC	1/70 (30) 0.5000	0/70 (24) NC
THYROID GLAND	ADENOMA, C-CELL, BENIGN	6/70 (33) 0.7226	9/70 (37) 0.3710	6/70 (32) 0.6019	4/70 (26) 0.7340
	ADENOMA, FOLLICULAR CELL, BENIGN	1/70 (31) 0.0056	0/70 (34) 1.0000	3/70 (30) 0.2937	5/70 (27) 0.0691
	CARCINOMA, FOLLICULAR CELL, MALIGNANT	1/70 (31) 0.1764	1/70 (34) 0.7764	0/70 (29) 1.0000	2/70 (25) 0.4185
Thymus	C_Thymoma Benign+Malignant	0/70 (30) 0.0413	0/70 (34) NC	1/70 (30) 0.5000	2/70 (25) 0.2020
Thyroid Gland	C_C cell adenoma+carcinoma	6/70 (33) 0.7226	9/70 (37) 0.3710	6/70 (32) 0.6019	4/70 (26) 0.7340
	C_Follicular cell adenoma+carcinoma	2/70 (32) 0.0096	1/70 (34) 0.8916	3/70 (30) 0.4687	6/70 (27) 0.0800
Whold Body	C_Hemangiosarcoma+Hemangioma	0/70 (30) 0.2635	1/70 (34) 0.5312	0/70 (29) NC	1/70 (24) 0.4444

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Water vs. Low	15 mg/kg/day Med (N=70) P-value - Water vs. Med	100 mg/kg/day High (N=70) P-value - Water vs. High
ZYMBAL'S GLAND	CARCINOMA, SEBACEOUS CELL, MALIGNANT	0/70 (30) 0.4576	0/70 (34) NC	1/70 (30) 0.5000	0/70 (24) NC
	PAPILLOMA, SQUAMOUS CELL, BENIGN	0/70 (30) 0.4298	0/70 (34) NC	2/70 (30) 0.2458	0/70 (24) NC

**Table 18: Tumor Rates and P-Values for Dose Response Relationship and
Pairwise Comparisons between the Vehicle Control and the Treated Groups-Male
Rats**

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	100 mg/kg/day High (N=70) P-value - Vehicle vs. High
ADRENAL GLANDS	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
	CARCINOMA, CORTICAL, MALIGNANT	0/70 (31) 0.4492	0/70 (34) NC	1/70 (29) 0.4833	0/70 (24) NC
	PHEOCHROMOCYTOMA, BENIGN	7/70 (33) 0.6673	4/70 (35) 0.9235	2/70 (30) 0.9808	3/70 (25) 0.8999
	PHEOCHROMOCYTOMA, COMPLEX, BENIGN	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
BONE MARROW, FEMUR	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (31) 0.7373	1/70 (34) 0.5231	0/70 (29) NC	0/70 (24) NC
BONE MARROW, STERN	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (31) 0.7373	1/70 (34) 0.5231	0/70 (29) NC	0/70 (24) NC
BONE, CRANIUM	OSTEOSARCOMA, MALIGNANT	1/70 (32) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
BONE, FEMUR	OSTEOSARCOMA, MALIGNANT	0/70 (31) 0.7373	1/70 (34) 0.5231	0/70 (29) NC	0/70 (24) NC
BRAIN	GLIOMA, MALIGNANT	1/70 (31) 0.9326	1/70 (34) 0.7764	0/70 (29) 1.0000	0/70 (24) 1.0000
	GRANULAR CELL TUMOR, BENIGN	1/70 (31) 0.7895	1/70 (34) 0.7764	1/70 (30) 0.7459	0/70 (24) 1.0000
	OLIGODENDROGLIOMA, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
HEART	SCHWANNOMA, ENDOCARDIAL, MALIGNANT	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
KIDNEYS	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
	LIPOMA, BENIGN	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
LIVER	ADENOMA, HEPATOCELLULAR, BENIGN	1/70 (32) 0.6945	0/70 (34) 1.0000	1/70 (29) 0.7290	0/70 (24) 1.0000
	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (31) 0.7373	1/70 (34) 0.5231	0/70 (29) NC	0/70 (24) NC
LUNG	ADENOMA, BRONCHIOLAR ALVEOLAR, BENIGN	0/70 (31) 0.7373	1/70 (34) 0.5231	0/70 (29) NC	0/70 (24) NC
	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	100 mg/kg/day High (N=70) P-value - Vehicle vs. High
LYMPH NODE, MEDIAS	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
Liver	C_Hepatocellular adenoma+carcinoma	1/70 (32) 0.6945	0/70 (34) 1.0000	1/70 (29) 0.7290	0/70 (24) 1.0000
MAMMARY GLAND	ADENOCARCINOMA, MALIGNANT	0/70 (31) 0.7373	1/70 (34) 0.5231	0/70 (29) NC	0/70 (24) NC
	FIBROADENOMA, BENIGN	1/70 (32) 0.4510	1/70 (34) 0.7688	0/70 (29) 1.0000	1/70 (24) 0.6779
MEDIASTINUM/PLE URA	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
MESENTERY/PERIT ONE	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
	LIPOMA, BENIGN	0/70 (31) 0.7373	1/70 (34) 0.5231	0/70 (29) NC	0/70 (24) NC
	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (31) 0.7373	1/70 (34) 0.5231	0/70 (29) NC	0/70 (24) NC
MULTICENTRIC NEOPL	HEMANGIOMA, BENIGN	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
	HEMANGIOSARCOMA, MALIGNANT	2/70 (31) 0.9832	1/70 (34) 0.8971	0/70 (29) 1.0000	0/70 (24) 1.0000
	LEUKEMIA, GRANULOCYTIC, MALIGNANT	1/70 (32) 0.1097	0/70 (34) 1.0000	0/70 (29) 1.0000	2/70 (25) 0.4067
	LYMPHOMA, MALIGNANT	0/70 (31) 0.3692	2/70 (35) 0.2774	0/70 (29) NC	1/70 (25) 0.4464
	MESOTHELIOMA, MALIGNANT	1/70 (32) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	SARCOMA, HISTIOCYTIC, MALIGNANT	0/70 (31) 0.4538	0/70 (34) NC	1/70 (30) 0.4918	0/70 (24) NC
NOSE	CARCINOMA, SQUAMOUS CELL, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
PANCREAS	ADENOMA, ACINAR CELL, BENIGN	2/70 (32) 0.5802	5/70 (36) 0.2658	3/70 (30) 0.4687	2/70 (25) 0.5950
	ADENOMA, ISLET CELL, BENIGN	2/70 (32) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	CARCINOMA, ACINAR CELL, MALIGNANT	1/70 (31) 0.3668	0/70 (34) 1.0000	0/70 (29) 1.0000	1/70 (24) 0.6869
	CARCINOMA, ISLET CELL, MALIGNANT	2/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (31) 0.7373	1/70 (34) 0.5231	0/70 (29) NC	0/70 (24) NC
PARATHYROID GLANDS	ADENOMA, BENIGN	2/70 (32) 0.8356	1/70 (34) 0.8916	2/70 (30) 0.6688	0/70 (24) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	100 mg/kg/day High (N=70) P-value - Vehicle vs. High
PITUITARY GLAND	ADENOMA, PARS DISTALIS, BENIGN	35/70 (49) 0.8378	40/70 (53) 0.4057	40/70 (50) 0.2237	26/70 (39) 0.7627
	ADENOMA, PARS INTERMEDIA, BENIGN	1/70 (31) 0.7037	0/70 (34) 1.0000	1/70 (30) 0.7459	0/70 (24) 1.0000
PROSTATE GLAND	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
Pancreas	C_Acinar cell+Islet cell adenoma	4/70 (33) 0.7375	5/70 (36) 0.5568	3/70 (30) 0.7456	2/70 (25) 0.8260
SEMINAL VESICLES	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
SKELETAL MUSCLE	FIBROSARCOMA, MALIGNANT	0/70 (31) 0.4492	0/70 (34) NC	1/70 (29) 0.4833	0/70 (24) NC
SKIN	KERATOACANTHOMA, BENIGN	1/70 (31) 0.9326	1/70 (34) 0.7764	0/70 (29) 1.0000	0/70 (24) 1.0000
	PAPILLOMA, SQUAMOUS CELL, BENIGN	0/70 (31) 0.6687	2/70 (35) 0.2774	1/70 (29) 0.4833	0/70 (24) NC
SKIN, SUBCUTIS	FIBROMA, BENIGN	6/70 (34) 0.8331	5/70 (36) 0.7761	2/70 (30) 0.9594	2/70 (25) 0.9312
	FIBROSARCOMA, MALIGNANT	2/70 (32) 0.2705	1/70 (34) 0.8916	0/70 (29) 1.0000	2/70 (25) 0.5950
	LIPOMA, BENIGN	2/70 (32) 0.4789	0/70 (34) 1.0000	1/70 (29) 0.8622	1/70 (24) 0.8211
	LIPOSARCOMA, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
	SCHWANNOMA, MALIGNANT	0/70 (31) 0.4492	0/70 (34) NC	1/70 (29) 0.4833	0/70 (24) NC
SMALL INTESTINE, D	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
SPLEEN	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (31) 0.7373	1/70 (34) 0.5231	0/70 (29) NC	0/70 (24) NC
	SARCOMA, UNDIFFERENTIATED, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
STOMACH	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (31) 0.2034	0/70 (34) NC	0/70 (29) NC	1/70 (24) 0.4364
	PAPILLOMA, SQUAMOUS CELL, BENIGN	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
Skin	C_Keratoacanthoma+Papilloma	1/70 (31) 0.9326	1/70 (34) 0.7764	0/70 (29) 1.0000	0/70 (24) 1.0000
TESTES	ADENOMA, LEYDIG CELL, BENIGN	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	ADENOMA, RETE TESTIS, BENIGN	0/70 (31) 0.7373	1/70 (34) 0.5231	0/70 (29) NC	0/70 (24) NC

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	100 mg/kg/day High (N=70) P-value - Vehicle vs. High
THYMUS	THYMOMA, BENIGN	0/70 (31) 0.0427	0/70 (34) NC	0/70 (29) NC	2/70 (25) 0.1948
	THYMOMA, MALIGNANT	0/70 (31) 0.4538	0/70 (34) NC	1/70 (30) 0.4918	0/70 (24) NC
THYROID GLAND	ADENOMA, C-CELL, BENIGN	8/70 (34) 0.8080	9/70 (37) 0.5798	6/70 (32) 0.7804	4/70 (26) 0.8664
	ADENOMA, FOLLICULAR CELL, BENIGN	3/70 (32) 0.0326	0/70 (34) 1.0000	3/70 (30) 0.6325	5/70 (27) 0.2606
	CARCINOMA, C-CELL, MALIGNANT	1/70 (31) 1.0000	0/70 (34) 1.0000	0/70 (29) 1.0000	0/70 (24) 1.0000
	CARCINOMA, FOLLICULAR CELL, MALIGNANT	0/70 (31) 0.0774	1/70 (34) 0.5231	0/70 (29) NC	2/70 (25) 0.1948
Thymus	C_Thymoma Benign+Malignant	0/70 (31) 0.0402	0/70 (34) NC	1/70 (30) 0.4918	2/70 (25) 0.1948
Thyroid Gland	C_C cell adenoma+carcinoma	9/70 (34) 0.8454	9/70 (37) 0.6848	6/70 (32) 0.8512	4/70 (26) 0.9131
	C_Follicular cell adenoma+carcinoma	3/70 (32) 0.0204	1/70 (34) 0.9501	3/70 (30) 0.6325	6/70 (27) 0.1579
Whold Body	C_Hemangiosarcoma+Hemangioma	2/70 (31) 0.5886	1/70 (34) 0.8971	0/70 (29) 1.0000	1/70 (24) 0.8287
ZYMBAL`S GLAND	CARCINOMA, SEBACEOUS CELL, MALIGNANT	0/70 (31) 0.4538	0/70 (34) NC	1/70 (30) 0.4918	0/70 (24) NC
	PAPILLOMA, SQUAMOUS CELL, BENIGN	0/70 (31) 0.4260	0/70 (34) NC	2/70 (30) 0.2377	0/70 (24) NC

**Table 19: Tumor Rates and P-Values for Dose Response Relationship and
Pairwise Comparisons between the Water Controls and the Treated Groups-
Female Rats**

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Water vs. Low	15 mg/kg/day Med (N=70) P-value - Water vs. Med	100 mg/kg/day High (N=70) P-value - Water vs. High
ADIPOSE TISSUE	HIBERNOMA, MALIGNANT	0/70 (40) 0.7561	1/70 (41) 0.5062	0/70 (41) NC	0/70 (42) NC
ADRENAL GLANDS	ADENOMA, CORTICAL, BENIGN	3/70 (41) 0.5631	2/70 (41) 0.8204	0/70 (41) 1.0000	2/70 (42) 0.8277
	CARCINOMA, CORTICAL, MALIGNANT	2/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	CARCINOMA, YOLK SAC, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	PHEOCHROMOCYTOMA, BENIGN	2/70 (41) 0.2070	7/70 (42) 0.0834	2/70 (41) 0.6922	6/70 (43) 0.1483
	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (40) 0.7561	1/70 (41) 0.5062	0/70 (41) NC	0/70 (42) NC
BONE	CARCINOMA, PARS DISTALIS, MALIGNANT	0/70 (40) 0.7561	1/70 (41) 0.5062	0/70 (41) NC	0/70 (42) NC
BONE MARROW, FEMUR	CARCINOMA, CORTICAL, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
BONE MARROW, STERN	CARCINOMA, CORTICAL, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
BRAIN	CARCINOMA, PARS DISTALIS, MALIGNANT	0/70 (40) 0.6364	1/70 (41) 0.5062	1/70 (42) 0.5122	0/70 (42) NC
	EPENDYMOMA, BENIGN	0/70 (40) 0.5091	0/70 (41) NC	1/70 (42) 0.5122	0/70 (42) NC
	GLIOMA, MALIGNANT	0/70 (40) 0.5603	3/70 (42) 0.1296	1/70 (42) 0.5122	1/70 (42) 0.5122
	GRANULAR CELL TUMOR, BENIGN	1/70 (40) 0.9416	1/70 (41) 0.7593	0/70 (41) 1.0000	0/70 (42) 1.0000
CLITORAL GLANDS	BASAL CELL TUMOR, BENIGN	0/70 (40) 0.2561	0/70 (41) NC	0/70 (41) NC	1/70 (42) 0.5122
	CARCINOMA, SQUAMOUS CELL, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
HEART	OSTEOSARCOMA, MALIGNANT	0/70 (40) 0.2561	0/70 (41) NC	0/70 (41) NC	1/70 (42) 0.5122
KIDNEYS	ADENOMA, TUBULAR CELL, BENIGN	0/70 (40) 0.2561	0/70 (41) NC	0/70 (41) NC	1/70 (42) 0.5122
	CARCINOMA, YOLK SAC, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Water vs. Low	15 mg/kg/day Med (N=70) P-value - Water vs. Med	100 mg/kg/day High (N=70) P-value - Water vs. High
	LIPOSARCOMA, MALIGNANT	0/70 (40) 0.5061	0/70 (41) NC	1/70 (41) 0.5062	0/70 (42) NC
LARGE INTESTINE, R	ADENOMA, BENIGN	0/70 (40) 0.2561	0/70 (41) NC	0/70 (41) NC	1/70 (42) 0.5122
LIVER	CARCINOMA, CORTICAL, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
LUNG	ADENOCARCINOMA, MALIGNANT	1/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	CARCINOMA, C-CELL, MALIGNANT	0/70 (40) 0.5061	0/70 (41) NC	1/70 (41) 0.5062	0/70 (42) NC
	CARCINOMA, CORTICAL, MALIGNANT	2/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	CARCINOMA, PARS DISTALIS, MALIGNANT	0/70 (40) 0.7561	1/70 (41) 0.5062	0/70 (41) NC	0/70 (42) NC
	CARCINOMA, SQUAMOUS CELL, MALIGNANT	1/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	HIBERNOMA, MALIGNANT	0/70 (40) 0.7561	1/70 (41) 0.5062	0/70 (41) NC	0/70 (42) NC
	OSTEOSARCOMA (PRIMARY SITE UNKNOWN), MAL	0/70 (40) 0.2561	0/70 (41) NC	0/70 (41) NC	1/70 (42) 0.5122
	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (40) 0.7561	1/70 (41) 0.5062	0/70 (41) NC	0/70 (42) NC
MAMMARY GLAND	ADENOCARCINOMA, MALIGNANT	23/70 (50) 0.9949	27/70 (53) 0.3805	17/70 (49) 0.9118	12/70 (48) 0.9917
	ADENOMA, BENIGN	1/70 (40) 0.6988	0/70 (41) 1.0000	2/70 (42) 0.5185	0/70 (42) 1.0000
	FIBROADENOMA, BENIGN	27/70 (49) 0.9345	26/70 (52) 0.7618	19/70 (48) 0.9588	18/70 (48) 0.9742
MEDIASTINUM/PLE URA	CARCINOMA, YOLK SAC, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
MESENTERY/PERIT ONE	CARCINOMA, SQUAMOUS CELL, MALIGNANT	1/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	CARCINOMA, YOLK SAC, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
MULTICENTRIC NEOPL	LEUKEMIA, GRANULOCYTIC, MALIGNANT	0/70 (40) 0.1978	0/70 (41) NC	1/70 (42) 0.5122	1/70 (43) 0.5181
	LYMPHOMA, MALIGNANT	5/70 (42) 0.3753	2/70 (42) 0.9454	1/70 (41) 0.9861	4/70 (44) 0.7812
	MESOTHELIOMA, MALIGNANT	0/70 (40) 0.2561	0/70 (41) NC	0/70 (41) NC	1/70 (42) 0.5122
	SARCOMA, HISTIOCYTIC, MALIGNANT	2/70 (41) 0.3767	1/70 (41) 0.8796	0/70 (41) 1.0000	2/70 (43) 0.7100

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Water vs. Low	15 mg/kg/day Med (N=70) P-value - Water vs. Med	100 mg/kg/day High (N=70) P-value - Water vs. High
NERVE, SCIATIC	SCHWANNOMA, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
OVARIES	ADENOMA, TUBULOSTROMAL, BENIGN	0/70 (40) 0.5061	0/70 (41) NC	1/70 (41) 0.5062	0/70 (42) NC
	CARCINOMA, YOLK SAC, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	SEX-CORD/STROMAL TUMOR, BENIGN	0/70 (40) 0.8182	2/70 (42) 0.2593	0/70 (41) NC	0/70 (42) NC
	SEX-CORD/STROMAL TUMOR, MALIGNANT	1/70 (40) 0.4024	0/70 (41) 1.0000	1/70 (41) 0.7593	1/70 (42) 0.7651
PANCREAS	ADENOMA, ACINAR CELL, BENIGN	0/70 (40) 0.0667	0/70 (41) NC	0/70 (41) NC	2/70 (43) 0.2654
	ADENOMA, ISLET CELL, BENIGN	0/70 (40) 0.7561	1/70 (41) 0.5062	0/70 (41) NC	0/70 (42) NC
	CARCINOMA, ACINAR CELL, MALIGNANT	0/70 (40) 0.3221	1/70 (41) 0.5062	0/70 (41) NC	1/70 (42) 0.5122
PARATHYROID GLANDS	ADENOMA, BENIGN	0/70 (40) 0.4501	2/70 (41) 0.2531	0/70 (41) NC	1/70 (42) 0.5122
PITUITARY GLAND	ADENOMA, PARS DISTALIS, BENIGN	41/70 (59) 0.8439	50/70 (61) 0.0832	39/70 (58) 0.6773	38/70 (57) 0.7004
	CARCINOMA, PARS DISTALIS, MALIGNANT	1/70 (41) 0.5232	1/70 (41) 0.7531	1/70 (42) 0.7590	1/70 (42) 0.7590
	C_ADENOMA++CARCINOMA	42/70 (59) 0.8361	51/70 (61) 0.0790	40/70 (59) 0.7255	39/70 (57) 0.7007
SKELETAL MUSCLE	SCHWANNOMA, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
SKIN	PAPILLOMA, SQUAMOUS CELL, BENIGN	0/70 (40) 0.3221	1/70 (41) 0.5062	0/70 (41) NC	1/70 (42) 0.5122
SKIN, SUBCUTIS	FIBROMA, BENIGN	0/70 (40) 0.3221	1/70 (41) 0.5062	0/70 (41) NC	1/70 (42) 0.5122
	FIBROSARCOMA, MALIGNANT	1/70 (40) 0.6140	2/70 (42) 0.5185	2/70 (42) 0.5185	1/70 (42) 0.7651
	LIPOMA, BENIGN	1/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	OSTEOSARCOMA, MALIGNANT	0/70 (40) 0.0667	0/70 (41) NC	0/70 (41) NC	2/70 (43) 0.2654
	SARCOMA, UNDIFFERENTIATED, MALIGNANT	0/70 (40) 0.1940	0/70 (41) NC	1/70 (42) 0.5122	1/70 (42) 0.5122
SMALL INTESTINE, J	CARCINOMA, SQUAMOUS CELL, MALIGNANT	1/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	LEIOMYOMA, BENIGN	0/70 (40) 0.3221	1/70 (41) 0.5062	0/70 (41) NC	1/70 (42) 0.5122

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Water vs. Low	15 mg/kg/day Med (N=70) P-value - Water vs. Med	100 mg/kg/day High (N=70) P-value - Water vs. High
SPLEEN	CARCINOMA, CORTICAL, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	CARCINOMA, YOLK SAC, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
STOMACH	CARCINOMA, SQUAMOUS CELL, MALIGNANT	1/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	CARCINOMA, YOLK SAC, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	PAPILLOMA, SQUAMOUS CELL, BENIGN	0/70 (40) 0.5091	0/70 (41) NC	1/70 (42) 0.5122	0/70 (42) NC
THYMUS	CARCINOMA, YOLK SAC, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	THYMOMA, BENIGN	0/70 (40) 0.5091	0/70 (41) NC	1/70 (42) 0.5122	0/70 (42) NC
THYROID GLAND	ADENOMA, C-CELL, BENIGN	8/70 (42) 0.7928	10/70 (44) 0.4394	6/70 (43) 0.8224	6/70 (43) 0.8224
	ADENOMA, FOLLICULAR CELL, BENIGN	0/70 (40) <0.001	1/70 (41) 0.5062	1/70 (41) 0.5062	8/70 (44) 0.0041
	CARCINOMA, C-CELL, MALIGNANT	0/70 (40) 0.5091	0/70 (41) NC	2/70 (41) 0.2531	0/70 (42) NC
	CARCINOMA, FOLLICULAR CELL, MALIGNANT	0/70 (40) 0.0032	1/70 (42) 0.5122	0/70 (41) NC	5/70 (43) 0.0332
Thyroid Gland	C_C cell adenoma+carcinoma	8/70 (42) 0.8082	10/70 (44) 0.4394	7/70 (43) 0.7317	6/70 (43) 0.8224
	C_Follicular cell adenoma+carcinoma	0/70 (40) <0.001	2/70 (42) 0.2593	1/70 (41) 0.5062	13/70 (45) <0.001
URINARY BLADDER	MESENCHYMAL PROLIFERATIVE LESION, BENIGN	1/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	PAPILLOMA, TRANSITIONAL CELL, BENIGN	0/70 (40) 0.7561	1/70 (41) 0.5062	0/70 (41) NC	0/70 (42) NC
UTERUS WITH CERVIX	ADENOCARCINOMA, MALIGNANT	0/70 (40) 0.0648	0/70 (41) NC	1/70 (41) 0.5062	2/70 (42) 0.2593
	CARCINOMA, SQUAMOUS CELL, MALIGNANT	1/70 (41) 0.4521	0/70 (41) 1.0000	0/70 (41) 1.0000	1/70 (43) 0.7648
	CARCINOMA, YOLK SAC, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	GRANULAR CELL TUMOR, BENIGN	1/70 (40) 0.7190	3/70 (41) 0.3172	3/70 (42) 0.3265	1/70 (42) 0.7651
	POLYP, GLANDULAR, BENIGN	0/70 (40) 0.3273	1/70 (41) 0.5062	0/70 (41) NC	1/70 (43) 0.5181
	POLYP, STROMAL, BENIGN	4/70 (42) 0.8922	2/70 (41) 0.8937	5/70 (43) 0.5152	1/70 (42) 0.9724

Organ Name	Tumor Name	0 mg/kg/day Water (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Water vs. Low	15 mg/kg/day Med (N=70) P-value - Water vs. Med	100 mg/kg/day High (N=70) P-value - Water vs. High
	SARCOMA, STROMAL, MALIGNANT	0/70 (40) 0.1970	0/70 (41) NC	1/70 (41) 0.5062	1/70 (43) 0.5181
	SARCOMA, UNDIFFERENTIATED, MALIGNANT	1/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	SCHWANNOMA, MALIGNANT	1/70 (40) 0.0696	0/70 (41) 1.0000	1/70 (42) 0.7651	3/70 (43) 0.3358
Uterus with cervix	C_stromal polyp+sarcoma	4/70 (42) 0.7795	2/70 (41) 0.8937	6/70 (43) 0.3844	2/70 (43) 0.9044
VAGINA	CARCINOMA, SQUAMOUS CELL, MALIGNANT	0/70 (40) 0.6349	1/70 (41) 0.5062	1/70 (41) 0.5062	0/70 (42) NC
	GRANULAR CELL TUMOR, BENIGN	5/70 (41) 0.9890	2/70 (41) 0.9456	3/70 (42) 0.8755	0/70 (42) 1.0000
	POLYP, BENIGN	0/70 (40) 0.2606	0/70 (41) NC	0/70 (41) NC	1/70 (43) 0.5181
	SARCOMA, STROMAL, MALIGNANT	0/70 (40) 0.2606	0/70 (41) NC	0/70 (41) NC	1/70 (43) 0.5181
	SCHWANNOMA, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
ZYMBAL'S GLAND	CARCINOMA, SQUAMOUS CELL, MALIGNANT	1/70 (40) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	FIBROSARCOMA, MALIGNANT	0/70 (40) 0.7576	1/70 (42) 0.5122	0/70 (41) NC	0/70 (42) NC

Table 20: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between the Vehicle Control and the Treated Groups-
Female Rats

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	100 mg/kg/day High (N=70) P-value - Vehicle vs. High
ADIPOSE TISSUE	HIBERNOMA, MALIGNANT	0/70 (41) 0.7515	1/70 (41) 0.5000	0/70 (41) NC	0/70 (42) NC
ADRENAL GLANDS	ADENOMA, CORTICAL, BENIGN	1/70 (42) 0.3329	2/70 (41) 0.4909	0/70 (41) 1.0000	2/70 (42) 0.5000
	PHEOCHROMOCYTOMA, BENIGN	0/70 (41) 0.0992	7/70 (42) 0.0065	2/70 (41) 0.2469	6/70 (43) 0.0150
	PHEOCHROMOCYTOMA, MALIGNANT	1/70 (42) 0.9371	1/70 (41) 0.7470	0/70 (41) 1.0000	0/70 (42) 1.0000
BONE	CARCINOMA, PARS DISTALIS, MALIGNANT	1/70 (42) 0.9371	1/70 (41) 0.7470	0/70 (41) 1.0000	0/70 (42) 1.0000
BRAIN	CARCINOMA, PARS DISTALIS, MALIGNANT	3/70 (42) 0.9718	1/70 (41) 0.9391	1/70 (42) 0.9420	0/70 (42) 1.0000
	EPENDYMOMA, BENIGN	0/70 (41) 0.5060	0/70 (41) NC	1/70 (42) 0.5060	0/70 (42) NC
	GLIOMA, MALIGNANT	4/70 (42) 0.9163	3/70 (42) 0.7837	1/70 (42) 0.9724	1/70 (42) 0.9724
	GRANULAR CELL TUMOR, BENIGN	0/70 (41) 0.7515	1/70 (41) 0.5000	0/70 (41) NC	0/70 (42) NC
	OLIGODENDROGLIOMA, MALIGNANT	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
CLITORAL GLANDS	BASAL CELL TUMOR, BENIGN	0/70 (41) 0.2545	0/70 (41) NC	0/70 (41) NC	1/70 (42) 0.5060
HEART	OSTEOSARCOMA, MALIGNANT	0/70 (41) 0.2545	0/70 (41) NC	0/70 (41) NC	1/70 (42) 0.5060
	SCHWANNOMA, ENDOCARDIAL, MALIGNANT	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
KIDNEYS	ADENOMA, TUBULAR CELL, BENIGN	0/70 (41) 0.2545	0/70 (41) NC	0/70 (41) NC	1/70 (42) 0.5060
	CARCINOMA, ACINAR CELL, MALIGNANT	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	LIPOSARCOMA, MALIGNANT	0/70 (41) 0.5030	0/70 (41) NC	1/70 (41) 0.5000	0/70 (42) NC
	ONCOCYTOMA, BENIGN	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
LARGE INTESTINE, R	ADENOMA, BENIGN	0/70 (41) 0.2545	0/70 (41) NC	0/70 (41) NC	1/70 (42) 0.5060
LIVER	CARCINOMA (PRIMARY SITE UNKNOWN), MALIGN	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	100 mg/kg/day High (N=70) P-value - Vehicle vs. High
	CARCINOMA, ACINAR CELL, MALIGNANT	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	CHOLANGIOMA, BENIGN	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
LUNG	CARCINOMA, C-CELL, MALIGNANT	1/70 (42) 0.7515	0/70 (41) 1.0000	1/70 (41) 0.7470	0/70 (42) 1.0000
	CARCINOMA, PARS DISTALIS, MALIGNANT	0/70 (41) 0.7515	1/70 (41) 0.5000	0/70 (41) NC	0/70 (42) NC
	HIBERNOMA, MALIGNANT	0/70 (41) 0.7515	1/70 (41) 0.5000	0/70 (41) NC	0/70 (42) NC
	OSTEOSARCOMA (PRIMARY SITE UNKNOWN), MAL	0/70 (41) 0.2545	0/70 (41) NC	0/70 (41) NC	1/70 (42) 0.5060
	PHEOCHROMOCYTOMA, MALIGNANT	0/70 (41) 0.7515	1/70 (41) 0.5000	0/70 (41) NC	0/70 (42) NC
MAMMARY GLAND	ADENOCARCINOMA, MALIGNANT	24/70 (51) 0.9957	27/70 (53) 0.4208	17/70 (49) 0.9281	12/70 (48) 0.9939
	ADENOMA, BENIGN	1/70 (42) 0.6920	0/70 (41) 1.0000	2/70 (42) 0.5000	0/70 (42) 1.0000
	FIBROADENOMA, BENIGN	33/70 (54) 0.9691	26/70 (52) 0.9111	19/70 (48) 0.9913	18/70 (48) 0.9952
MESENTERY/PERIT ONE	CARCINOMA, ACINAR CELL, MALIGNANT	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
MULTICENTRIC NEOPL	HEMANGIOMA, BENIGN	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	LEUKEMIA, GRANULOCYTIC, MALIGNANT	0/70 (41) 0.1954	0/70 (41) NC	1/70 (42) 0.5060	1/70 (43) 0.5119
	LYMPHOMA, MALIGNANT	2/70 (42) 0.1505	2/70 (42) 0.6921	1/70 (41) 0.8751	4/70 (44) 0.3606
	MESOTHELIOMA, MALIGNANT	0/70 (41) 0.2545	0/70 (41) NC	0/70 (41) NC	1/70 (42) 0.5060
	SARCOMA, HISTIOCYTIC, MALIGNANT	0/70 (41) 0.1154	1/70 (41) 0.5000	0/70 (41) NC	2/70 (43) 0.2590
OVARIES	ADENOMA, TUBULOSTROMAL, BENIGN	0/70 (41) 0.5030	0/70 (41) NC	1/70 (41) 0.5000	0/70 (42) NC
	SEX-CORD/STROMAL TUMOR, BENIGN	1/70 (42) 0.9375	2/70 (42) 0.5000	0/70 (41) 1.0000	0/70 (42) 1.0000
	SEX-CORD/STROMAL TUMOR, MALIGNANT	0/70 (41) 0.1909	0/70 (41) NC	1/70 (41) 0.5000	1/70 (42) 0.5060
PANCREAS	ADENOMA, ACINAR CELL, BENIGN	2/70 (42) 0.2732	0/70 (41) 1.0000	0/70 (41) 1.0000	2/70 (43) 0.7009
	ADENOMA, ISLET CELL, BENIGN	0/70 (41) 0.7515	1/70 (41) 0.5000	0/70 (41) NC	0/70 (42) NC

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	100 mg/kg/day High (N=70) P-value - Vehicle vs. High
	CARCINOMA, ACINAR CELL, MALIGNANT	1/70 (42) 0.5375	1/70 (41) 0.7470	0/70 (41) 1.0000	1/70 (42) 0.7530
PARATHYROID GLANDS	ADENOMA, BENIGN	3/70 (43) 0.8203	2/70 (41) 0.8049	0/70 (41) 1.0000	1/70 (42) 0.9391
PITUITARY GLAND	ADENOMA, PARS DISTALIS, BENIGN	48/70 (60) 0.9536	50/70 (61) 0.4823	39/70 (58) 0.9631	38/70 (57) 0.9677
	CARCINOMA, PARS DISTALIS, MALIGNANT	3/70 (42) 0.7856	1/70 (41) 0.9391	1/70 (42) 0.9420	1/70 (42) 0.9420
	C_ADENOMA++CARCINOMA	51/70 (61) 0.9637	51/70 (61) 0.5963	40/70 (59) 0.9877	39/70 (57) 0.9848
	GLIOMA, MALIGNANT	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
SKIN	PAPILLOMA, SQUAMOUS CELL, BENIGN	1/70 (42) 0.5375	1/70 (41) 0.7470	0/70 (41) 1.0000	1/70 (42) 0.7530
SKIN, SUBCUTIS	FIBROMA, BENIGN	2/70 (43) 0.6734	1/70 (41) 0.8705	0/70 (41) 1.0000	1/70 (42) 0.8751
	FIBROSARCOMA, MALIGNANT	1/70 (42) 0.6022	2/70 (42) 0.5000	2/70 (42) 0.5000	1/70 (42) 0.7530
	LIPOSARCOMA, MALIGNANT	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	OSTEOSARCOMA, MALIGNANT	0/70 (41) 0.0659	0/70 (41) NC	0/70 (41) NC	2/70 (43) 0.2590
	SARCOMA, UNDIFFERENTIATED, MALIGNANT	0/70 (41) 0.1917	0/70 (41) NC	1/70 (42) 0.5060	1/70 (42) 0.5060
SMALL INTESTINE, J	LEIOMYOMA, BENIGN	0/70 (41) 0.3182	1/70 (41) 0.5000	0/70 (41) NC	1/70 (42) 0.5060
STOMACH	CARCINOMA, ACINAR CELL, MALIGNANT	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	CARCINOMA, SQUAMOUS CELL, MALIGNANT	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	PAPILLOMA, SQUAMOUS CELL, BENIGN	1/70 (42) 0.7545	0/70 (41) 1.0000	1/70 (42) 0.7530	0/70 (42) 1.0000
THYMUS	THYMOMA, BENIGN	0/70 (41) 0.5060	0/70 (41) NC	1/70 (42) 0.5060	0/70 (42) NC
THYROID GLAND	ADENOMA, C-CELL, BENIGN	7/70 (42) 0.7480	10/70 (44) 0.3328	6/70 (43) 0.7412	6/70 (43) 0.7412
	ADENOMA, FOLLICULAR CELL, BENIGN	2/70 (42) 0.0021	1/70 (41) 0.8751	1/70 (41) 0.8751	8/70 (44) 0.0522
	CARCINOMA, C-CELL, MALIGNANT	1/70 (42) 0.6909	0/70 (41) 1.0000	2/70 (41) 0.4909	0/70 (42) 1.0000
	CARCINOMA, FOLLICULAR CELL, MALIGNANT	0/70 (41) 0.0031	1/70 (42) 0.5060	0/70 (41) NC	5/70 (43) 0.0312

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=70) P-value - Trend	5 mg/kg/day Low (N=70) P-value - Vehicle vs. Low	15 mg/kg/day Med (N=70) P-value - Vehicle vs. Med	100 mg/kg/day High (N=70) P-value - Vehicle vs. High
Thyroid Gland	C_C cell adenoma+carcinoma	8/70 (42) 0.8082	10/70 (44) 0.4394	7/70 (43) 0.7317	6/70 (43) 0.8224
	C_Follicular cell adenoma+carcinoma	2/70 (42) <0.001	2/70 (42) 0.6921	1/70 (41) 0.8751	13/70 (45) 0.0027
URINARY BLADDER	CARCINOMA, ACINAR CELL, MALIGNANT	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	PAPILLOMA, TRANSITIONAL CELL, BENIGN	0/70 (41) 0.7515	1/70 (41) 0.5000	0/70 (41) NC	0/70 (42) NC
UTERUS WITH CERVIX	ADENOCARCINOMA, MALIGNANT	3/70 (43) 0.4286	0/70 (41) 1.0000	1/70 (41) 0.9360	2/70 (42) 0.8126
	CARCINOMA, ACINAR CELL, MALIGNANT	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	CARCINOMA, SQUAMOUS CELL, MALIGNANT	1/70 (42) 0.4498	0/70 (41) 1.0000	0/70 (41) 1.0000	1/70 (43) 0.7588
	GRANULAR CELL TUMOR, BENIGN	4/70 (42) 0.9160	3/70 (41) 0.7737	3/70 (42) 0.7837	1/70 (42) 0.9724
	POLYP, GLANDULAR, BENIGN	2/70 (42) 0.6841	1/70 (41) 0.8751	0/70 (41) 1.0000	1/70 (43) 0.8838
	POLYP, STROMAL, BENIGN	3/70 (43) 0.8412	2/70 (41) 0.8049	5/70 (43) 0.3565	1/70 (42) 0.9391
	SARCOMA, STROMAL, MALIGNANT	2/70 (42) 0.5881	0/70 (41) 1.0000	1/70 (41) 0.8751	1/70 (43) 0.8838
	SCHWANNOMA, MALIGNANT	0/70 (41) 0.0205	0/70 (41) NC	1/70 (42) 0.5060	3/70 (43) 0.1295
Uterus with cervix	C_stromal polyp+sarcoma	5/70 (43) 0.8303	2/70 (41) 0.9377	6/70 (43) 0.5000	2/70 (43) 0.9452
VAGINA	CARCINOMA, SQUAMOUS CELL, MALIGNANT	0/70 (41) 0.6303	1/70 (41) 0.5000	1/70 (41) 0.5000	0/70 (42) NC
	GRANULAR CELL TUMOR, BENIGN	3/70 (42) 0.9549	2/70 (41) 0.8126	3/70 (42) 0.6621	0/70 (42) 1.0000
	POLYP, BENIGN	1/70 (42) 0.4498	0/70 (41) 1.0000	0/70 (41) 1.0000	1/70 (43) 0.7588
	SARCOMA, STROMAL, MALIGNANT	0/70 (41) 0.2590	0/70 (41) NC	0/70 (41) NC	1/70 (43) 0.5119
Whold Body	C_Hemangiosarcoma+Hemangioma	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
ZYMBAL`S GLAND	CARCINOMA, SEBACEOUS CELL, MALIGNANT	1/70 (42) 1.0000	0/70 (41) 1.0000	0/70 (41) 1.0000	0/70 (42) 1.0000
	FIBROSARCOMA, MALIGNANT	0/70 (41) 0.7530	1/70 (42) 0.5060	0/70 (41) NC	0/70 (42) NC

Table 21: Intercurrent Mortality Rate -Male Mice

	0 mg/kg/day Water (N=25)		0 mg/kg/day Vehicle (N=35)		15 mg/kg/day Low (N=35)		50 mg/kg/day Med (N=35)		500 mg/kg/day High (N=35)		1500 mg/kg/day High2 (N=35)		75 mg/kg/day Positive (N=10)	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	.	.	.	.	2	5.71	1	2.86	1	2.86	1	2.86	.	.
14 - 26	2	8.00	3	8.71	1	8.57	1	5.71	2	8.57	1	5.71	2	5.71
Ter. Sac.	23	92.00	32	91.29	32	91.43	33	94.29	32	91.43	33	94.29	8	22.86

Table 22: Intercurrent Mortality Rate -Female Mice

	0 mg/kg/day Water (N=25)		0 mg/kg/day Vehicle (N=35)		15 mg/kg/day Low (N=35)		50 mg/kg/day Med (N=35)		500 mg/kg/day High (N=35)		1500 mg/kg/day High2 (N=35)		75 mg/kg/day Positive (N=10)	
Week	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %	No. of Death	Cum. %
0 - 13	.	.	1	2.86	.	.	1	2.86	.	.	.	.	.	.
14 - 26	.	.	3	10.57	3	8.57	2	8.57	.	.	.	.	1	2.86
Ter. Sac.	25	100.00	31	89.43	32	91.43	32	91.43	35	100.00	35	100.00	9	25.71

Table 23: Intercurrent Mortality Comparison between Treated Groups and Water Control-Male Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. High 2	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.7654	0.9050	0.7570	0.9179	0.7570	0.3073
Homogeneity	Log-Rank	0.9802	0.9050	0.7556	0.9178	0.7556	0.2753

Table 24: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control-Male Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. High 2	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.7307	0.9610	0.6726	0.9710	0.6726	0.3051
Homogeneity	Log-Rank	0.9769	0.9609	0.6738	0.9709	0.6738	0.2623

Table 25: Intercurrent Mortality Comparison between Treated Groups and Water Control- Female Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. High 2	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.4980	0.0689	0.0689	.	.	0.1134
Homogeneity	Log-Rank	0.0765	0.1374	0.1374	.	.	0.1138

Table 26: Intercurrent Mortality Comparison between Treated Groups and Vehicle Control-Female Mice

Test	Statistic	P_Value Vehicle vs Treated Groups Dose Response	P_Value Vehicle vs. Low	P_Value Vehicle vs. Med	P_Value Vehicle vs. High	P_Value Vehicle vs. High 2	P_Value Vehicle vs. Positive
Dose-Response	Likelihood Ratio	0.0251	0.6840	0.7089	0.0167	0.0167	0.8844
Homogeneity	Log-Rank	0.1193	0.6845	0.7094	0.0408	0.0408	0.8855

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Table 27: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	15 mg/kg/day Low (N=35) P-value - Vehicle vs. Low	50 mg/kg/day Med (N=35) P-value - Vehicle vs. Low	500 mg/kg/day High (N=35) P-value - Vehicle vs. Med	1500 mg/kg/day High 2 (N=35) P-value - Vehicle vs. High
HARDERIAN GLANDS	ADENOMA, BENIGN	0/35 (35) 0.1028	1/35 (32) 0.4776	0/35 (34) NC	2/35 (33) 0.2318	0/35 (34) NC
LUNG	ADENOMA, BRONCHIOLAR ALVEOLAR, BENIGN	1/35 (35) 0.0595	0/35 (32) 1.0000	1/35 (34) 0.7464	3/35 (33) 0.2847	0/35 (34) 1.0000
	CARCINOMA, BRONCHIOLAR ALVEOLAR, MALIGNANT	1/35 (35) 0.7519	0/35 (32) 1.0000	1/35 (34) 0.7464	0/35 (33) 1.0000	0/35 (34) 1.0000
LYMPH NODE, INGUIN	LYMPHANGIOMA, BENIGN	0/35 (35) 0.7388	1/35 (32) 0.4776	0/35 (34) NC	0/35 (33) NC	0/35 (34) NC
Lung	C_Bronchiolar alveolar adenoma+carcinoma	2/35 (35) 0.1321	0/35 (32) 1.0000	2/35 (34) 0.6820	3/35 (33) 0.4716	0/35 (34) 1.0000
MULTICENTRIC NEOPL	HEMANGIOSARCOMA, MALIGNANT	2/35 (35) 0.6424	1/35 (32) 0.8634	2/35 (34) 0.6820	1/35 (33) 0.8694	2/35 (34) 0.6820
	LYMPHOMA, MALIGNANT	0/35 (35) 0.5000	0/35 (32) NC	1/35 (34) 0.4928	0/35 (33) NC	1/35 (34) 0.4853
	MESOTHELIOMA, MALIGNANT	1/35 (35) 1.0000	0/35 (32) 1.0000	0/35 (34) 1.0000	0/35 (33) 1.0000	0/35 (34) 1.0000
SKIN	PAPILLOMA, BENIGN	0/35 (35) 0.2463	0/35 (32) NC	0/35 (34) NC	1/35 (33) 0.4853	0/35 (33) NC
STOMACH	PAPILLOMA, BENIGN	1/35 (35) 0.6163	2/35 (32) 0.4659	0/35 (34) 1.0000	1/35 (33) 0.7388	0/35 (34) 1.0000

Table 28: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and the Treated Groups-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25) P-value - Trend	15 mg/kg/day Low (N=35) P-value - Water vs. Low	50 mg/kg/day Med (N=35) P-value - Water vs. Low	500 mg/kg/day High (N=35) P-value - Water vs. Med	1500 mg/kg/day High 2 (N=35) P-value - Water vs. High
HARDERIAN GLANDS	ADENOMA, BENIGN	0/25 (33) 0.1300	1/35 (25) 0.5614	0/35 (32) NC	2/35 (34) 0.3194	0/35 (34) NC
LUNG	ADENOMA, BRONCHIOLAR ALVEOLAR, BENIGN	5/25 (33) 0.4384	0/35 (25) 1.0000	1/35 (32) 0.9961	3/35 (34) 0.9424	0/35 (34) 1.0000
	CARCINOMA, BRONCHIOLAR ALVEOLAR, MALIGNANT	1/25 (33) 0.7907	0/35 (25) 1.0000	1/35 (32) 0.8247	0/35 (34) 1.0000	0/35 (34) 1.0000
LYMPH NODE, INGUIN	LYMPHANGIOMA, BENIGN	0/25 (33) 0.7984	1/35 (25) 0.5614	0/35 (32) NC	0/35 (34) NC	0/35 (34) NC
Lung	C_Bronchiolar alveolar adenoma+carcinoma	6/25 (33) 0.5864	0/35 (25) 1.0000	2/35 (32) 0.9921	3/35 (34) 0.9726	0/35 (34) 1.0000
MULTICENTRIC NEOPL	HEMANGIOSARCOMA, MALIGNANT	2/25 (33) 0.7110	1/35 (25) 0.9214	2/35 (32) 0.8004	1/35 (34) 0.9255	2/35 (34) 0.8004
	LYMPHOMA, MALIGNANT	0/25 (33) 0.5403	0/35 (25) NC	1/35 (32) 0.5763	0/35 (34) NC	1/35 (34) 0.5690
	MESOTHELIOMA, MALIGNANT	1/25 (33) 1.0000	0/35 (25) 1.0000	0/35 (32) 1.0000	0/35 (34) 1.0000	0/35 (34) 1.0000
SKIN	PAPILLOMA, BENIGN	0/25 (33) 0.2661	0/35 (25) NC	0/35 (32) NC	1/35 (34) 0.5690	0/35 (34) NC
STOMACH	CARCINOMA, SQUAMOUS CELL, MALIGNANT	1/25 (33) 1.0000	0/35 (25) 1.0000	0/35 (32) 1.0000	0/35 (34) 1.0000	0/35 (34) 1.0000
	PAPILLOMA, BENIGN	0/25 (33) 0.4912	2/35 (25) 0.3108	0/35 (32) NC	1/35 (34) 0.5690	0/35 (34) NC

Table 29: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	75 mg/kg/day Positive (N=10) P-value - Water vs. Positive
LUNG	ADENOMA, BRONCHIOLAR ALVEOLAR, BENIGN	5/25 (25)	1/10 (10) 0.8909
	CARCINOMA, BRONCHIOLAR ALVEOLAR, MALIGNANT	1/25 (25)	1/10 (9) 0.4652
Lung	C_Bronchiolar alveolar adenoma+carcinoma	6/25 (25)	2/10 (10) 0.7498
MULTICENTRIC NEOPL	HEMANGIOSARCOMA, MALIGNANT	2/25 (25)	2/10 (9) 0.2809
	LYMPHOMA, MALIGNANT	0/25 (25)	1/10 (10) 0.2857
SKIN	PAPILLOMA, BENIGN	0/25 (25)	4/10 (9) 0.0027
STOMACH	PAPILLOMA, BENIGN	0/25 (25)	8/10 (9) <0.001

Table 30: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and Positive Control-Male Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=35)	75 mg/kg/day Positive (N=10) P-value - Vehicle vs. Positive
LUNG	ADENOMA, BRONCHIOLAR ALVEOLAR, BENIGN	1/35 (35)	1/10 (10) 0.3990
	CARCINOMA, BRONCHIOLAR ALVEOLAR, MALIGNANT	1/35 (35)	1/10 (9) 0.3710
Lung	C_Bronchiolar alveolar adenoma+carcinoma	2/35 (35)	2/10 (10) 0.2093
MULTICENTRIC NEOPL	HEMANGIOSARCOMA, MALIGNANT	2/35 (35)	2/10 (9) 0.1804
	LYMPHOMA, MALIGNANT	0/35 (35)	1/10 (10) 0.2222
	MESOTHELIOMA, MALIGNANT	1/35 (35)	0/10 (9) 1.0000
SKIN	PAPILLOMA, BENIGN	0/35 (35)	4/10 (9) <0.001
STOMACH	PAPILLOMA, BENIGN	1/35 (35)	8/10 (9) <0.001

Table 31: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and the Treated Groups-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25) P-value - Trend	15 mg/kg/day Low (N=35) P-value - Water vs. Low	50 mg/kg/day Med (N=35) P-value - Water vs. Low	500 mg/kg/day High (N=35) P-value - Water vs. Med	1500 mg/kg/day High 2 (N=35) P-value - Water vs. High
HARDERIAN GLANDS	ADENOCARCINOMA, MALIGNANT	1/25 (35) 1.0000	0/35 (25) 1.0000	0/35 (34) 1.0000	0/35 (33) 1.0000	0/35 (33) 1.0000
	ADENOMA, BENIGN	0/25 (35) 0.3675	1/35 (25) 0.5763	0/35 (34) NC	1/35 (33) 0.5833	0/35 (33) NC
LUNG	ADENOMA, BRONCHIOLAR ALVEOLAR, BENIGN	1/25 (35) 0.9160	2/35 (25) 0.6155	1/35 (34) 0.8185	0/35 (33) 1.0000	2/35 (33) 0.6259
	CARCINOMA, BRONCHIOLAR ALVEOLAR, MALIGNA	0/25 (35) 0.8031	1/35 (25) 0.5763	0/35 (34) NC	0/35 (33) NC	0/35 (33) NC
Lung	C_Bronchiolar alveolar adenoma+carcinoma	1/25 (35) 0.9467	3/35 (25) 0.4306	1/35 (34) 0.8185	0/35 (33) 1.0000	2/35 (33) 0.6259
MULTICENTRIC NEOPL	HEMANGIOSARCOMA, MALIGNANT	2/25 (35) 0.7243	4/35 (25) 0.5083	1/35 (35) 0.9255	2/35 (33) 0.8090	3/35 (33) 0.6586
SKIN	PAPILLOMA, BENIGN	1/25 (35) 1.0000	0/35 (25) 1.0000	0/35 (34) 1.0000	0/35 (33) 1.0000	0/35 (33) 1.0000
STOMACH	PAPILLOMA, BENIGN	0/25 (35) 0.8031	1/35 (25) 0.5763	0/35 (34) NC	0/35 (33) NC	0/35 (33) NC
THYMUS	THYMOMA, MALIGNANT	1/25 (35) 0.4768	0/35 (25) 1.0000	0/35 (34) 1.0000	1/35 (33) 0.8305	0/35 (33) 1.0000

Table 32: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and the Treated Groups-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=25) P-value - Trend	15 mg/kg/day Low (N=35) P-value - Vehicle vs. Low	50 mg/kg/day Med (N=35) P-value - Vehicle vs. Low	500 mg/kg/day High (N=35) P-value - Vehicle vs. Med	1500 mg/kg/day High 2 (N=35) P-value - Vehicle vs. High
HARDERIAN GLANDS	ADENOMA, BENIGN	1/35 (35) 0.5507	1/35 (33) 0.7612	0/35 (34) 1.0000	1/35 (33) 0.7682	0/35 (33) 1.0000
LUNG	ADENOMA, BRONCHIOLAR ALVEOLAR, BENIGN	0/35 (35) 0.7447	2/35 (33) 0.2537	1/35 (34) 0.5000	0/35 (33) NC	2/35 (33) 0.2612
	CARCINOMA, BRONCHIOLAR ALVEOLAR, MALIGNA	1/35 (35) 0.9389	1/35 (34) 0.7537	0/35 (34) 1.0000	0/35 (33) 1.0000	0/35 (33) 1.0000
Lung	C_Bronchiolar alveolar adenoma+carcinoma	1/35 (35) 0.9193	3/35 (34) 0.3068	1/35 (34) 0.7463	0/35 (33) 1.0000	2/35 (33) 0.5110
MESENTERY	MESOTHELIOMA, MALIGNANT	1/35 (35) 1.0000	0/35 (34) 1.0000	0/35 (34) 1.0000	0/35 (33) 1.0000	0/35 (33) 1.0000
MULTICENTRIC NEOPL	HEMANGIOSARCOMA, MALIGNANT	1/35 (35) 0.5553	4/35 (33) 0.1969	1/35 (35) 0.7538	2/35 (33) 0.5224	3/35 (33) 0.3295
STOMACH	PAPILLOMA, BENIGN	1/35 (35) 0.9416	1/35 (33) 0.7612	0/35 (34) 1.0000	0/35 (33) 1.0000	0/35 (33) 1.0000
THYMUS	THYMOMA, MALIGNANT	0/35 (35) 0.2593	0/35 (33) NC	0/35 (34) NC	1/35 (33) 0.5147	0/35 (34) NC

Table 33: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Water Control and Positive Control-Female Mice

Organ Name	Tumor Name	0 mg/kg/day Water (N=25)	75 mg/kg/day Positive (N=10) P-value - Water vs. Positive
MULTICENTRIC NEOPL	HEMANGIOSARCOMA, MALIGNANT	2/25 (25)	1/10 (10) 0.6486
	LYMPHOMA, MALIGNANT	0/25 (25)	1/10 (10) 0.2857
SKIN	PAPILLOMA, BENIGN	1/25 (25)	6/10 (10) <0.001
STOMACH	PAPILLOMA, BENIGN	0/25 (25)	10/10 (10) <0.001

Table 34: Tumor Rates and P-Values for Dose Response Relationship and Pairwise Comparisons between Vehicle Control and Positive Control- Female Mice

Organ Name	Tumor Name	0 mg/kg/day Vehicle (N=35)	75 mg/kg/day Positive (N=10) P-value - Vehicle vs. Positive
MULTICENTRIC NEOPL	HEMANGIOSARCOMA, MALIGNANT	1/35 (33)	1/10 (10) 0.4153
	LYMPHOMA, MALIGNANT	0/35 (33)	1/10 (10) 0.2326
SKIN	PAPILLOMA, BENIGN	0/35 (33)	6/10 (10) <0.001
STOMACH	PAPILLOMA, BENIGN	1/35 (33)	10/10 (10) <0.001

Figure 1: Kaplan-Meier Survival Functions for Male Rats

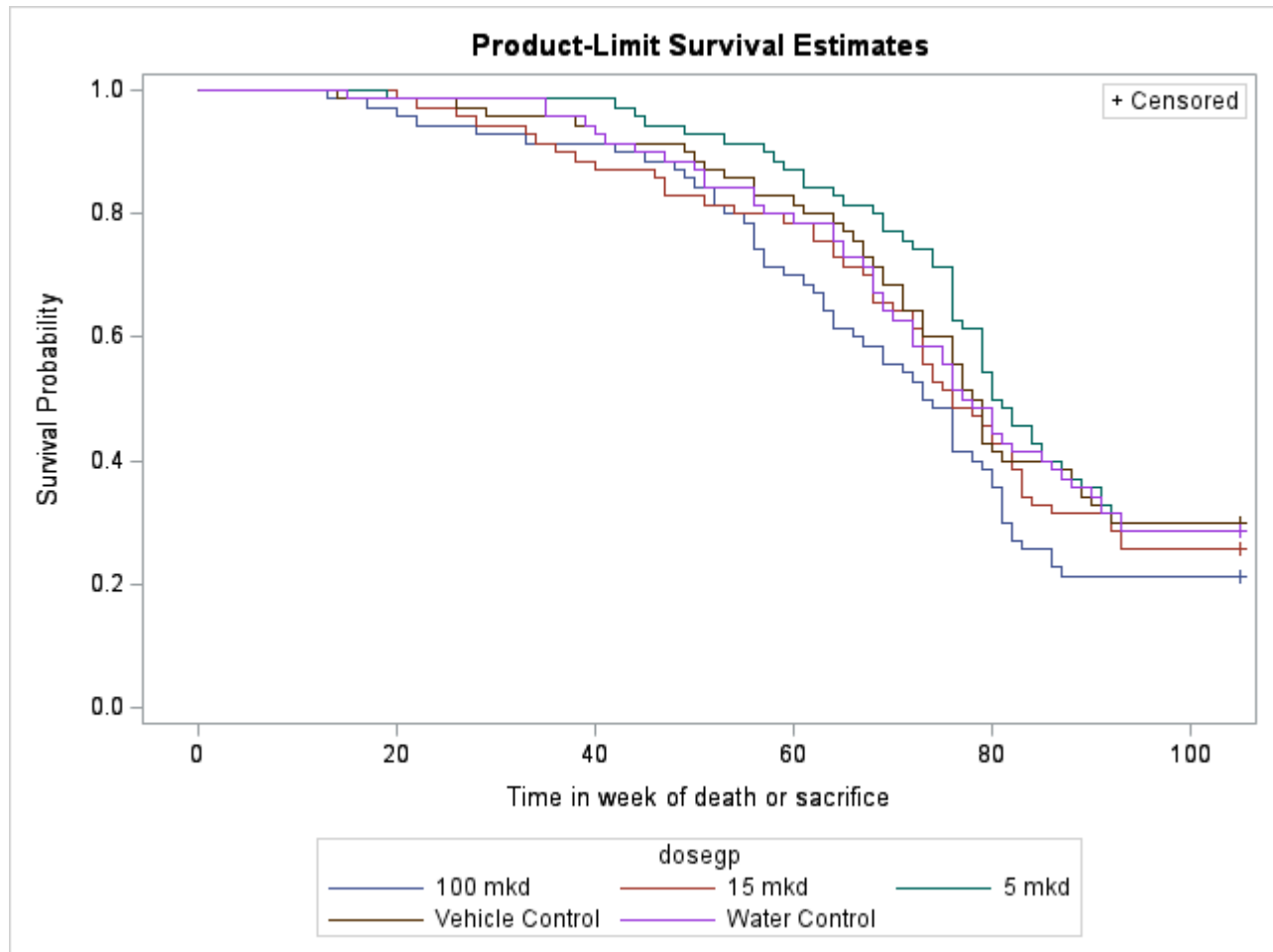


Figure 2: Kaplan-Meier Survival Functions for Female Rats

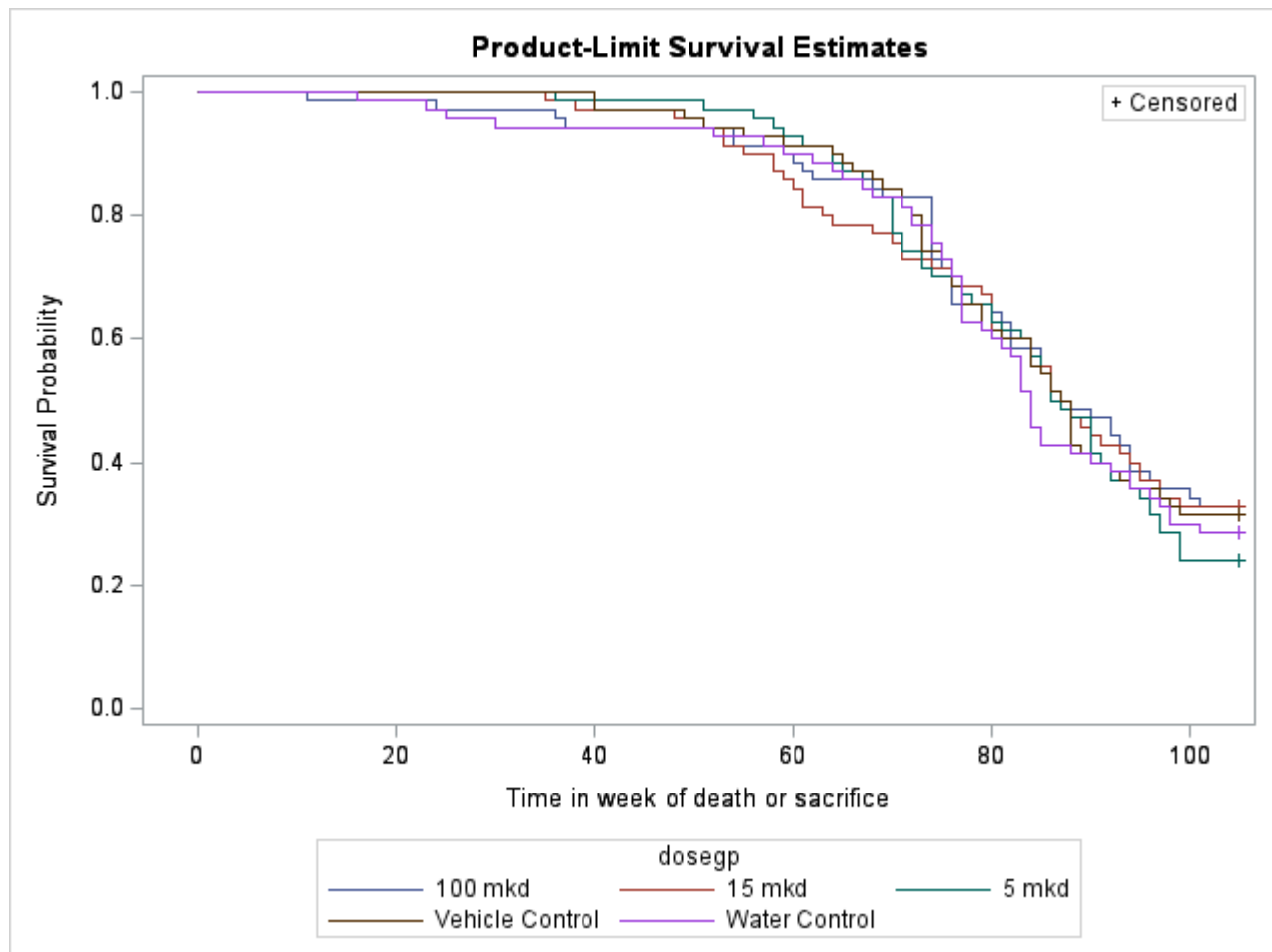


Figure 3: Kaplan-Meier Survival Functions for Male Mice

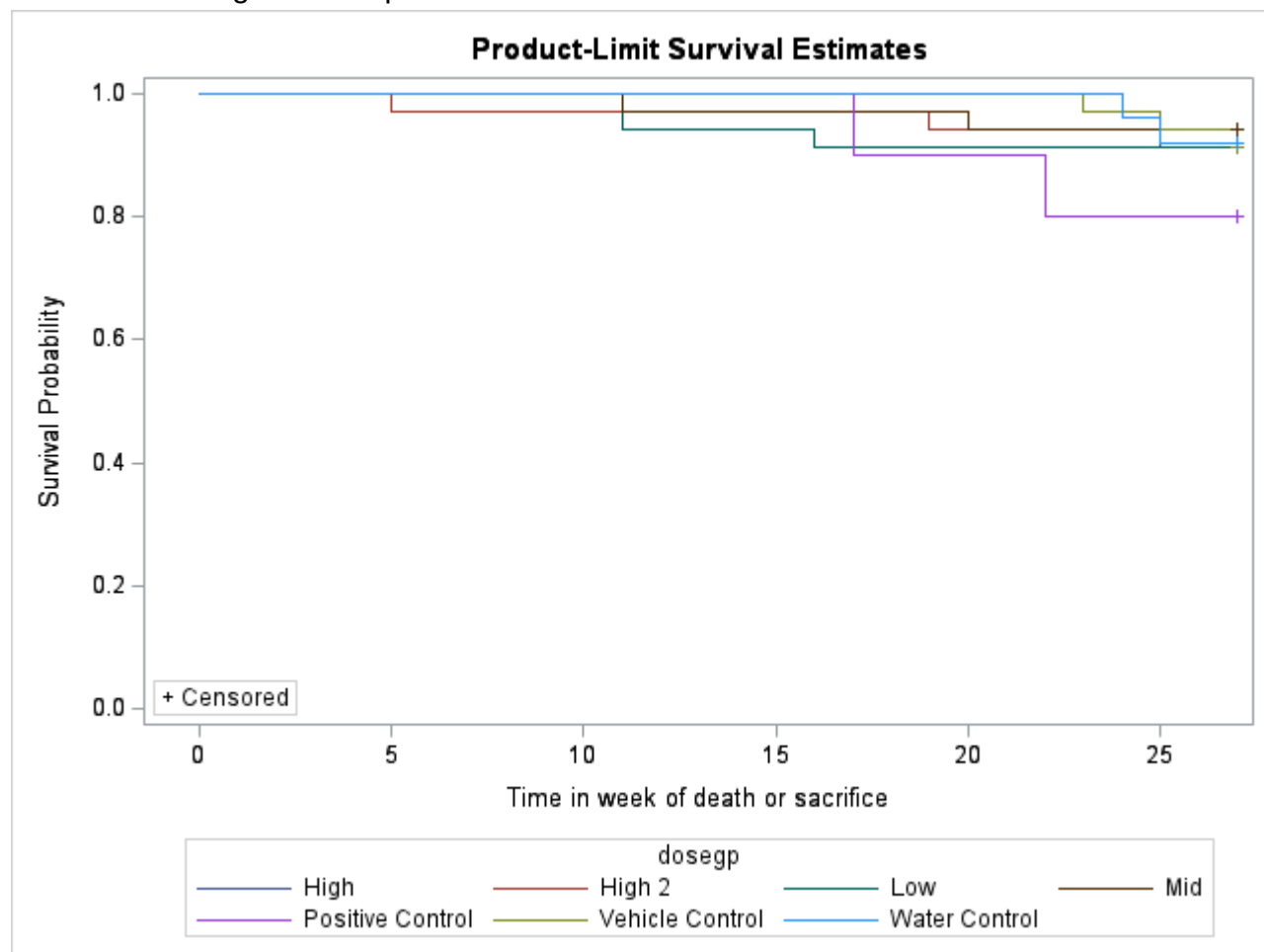
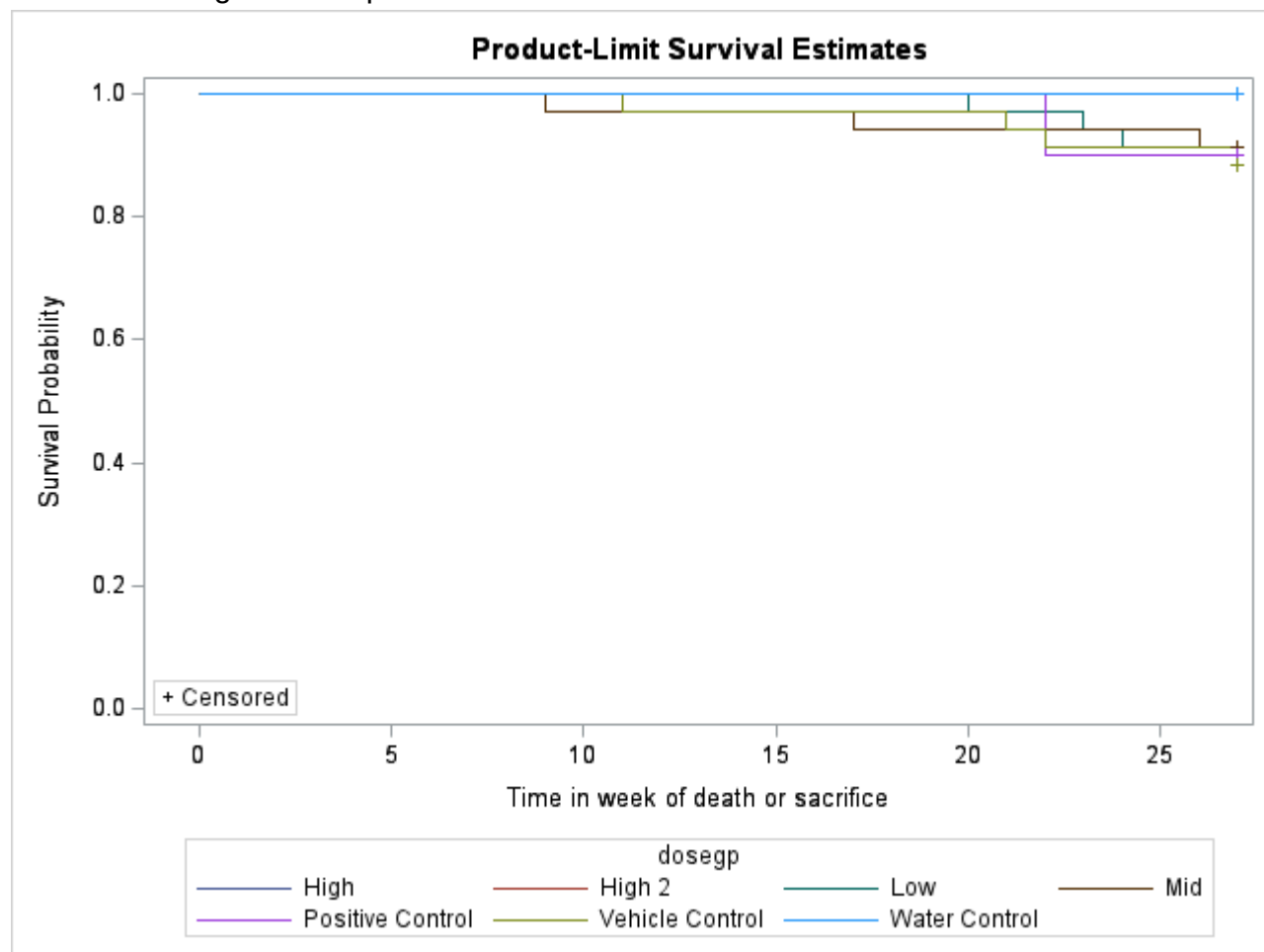


Figure 4: Kaplan-Meier Survival Functions for Female Mice



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