CLINICAL STUDY PROTOCOL

Final Version Date: 10 May 2019

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

Study No.: NBI-74788-CAH2008

Development Phase: Phase 2

Sponsor: Neurocrine Biosciences, Inc.
12780 El Camino Real
San Diego, CA 92130
Telephone: (858) 617-7600
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SIGNATURES:

I agree to conduct this study in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- Established principles of Good Clinical Practice (GCP) (Harmonized)
- United States (US) Code of Federal Regulations (CFR); US Food and Drug Administration (FDA)
- Canada Food and Drugs Act and Regulations; Health Canada

CLINICAL STUDY TITLE:

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

Study No.: NBI-74788-CAH2008

As Agreed:

_____ _____

Principal Investigator Signature Date

PRINCIPAL INVESTIGATOR:

_____

(Print Principal Investigator Name)

SITE:

_____

(Print Site Name)

Accepted for the Sponsor:

SPONSOR: Neurocrine Biosciences, Inc.
12780 El Camino Real
San Diego, CA 92130
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Date [redacted]

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1. SYNOPSIS

Title of study: 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

Study number: NBI-74788-CAH2008

Study center(s): Approximately 5 study centers in North America

Objectives:

- To assess the safety and tolerability of NBI-74788 in pediatric subjects 14 to 17 years of age with congenital adrenal hyperplasia (CAH).
- To evaluate the effect of repeated doses of NBI-74788 on endogenous levels of pharmacodynamic (PD) biomarkers in pediatric subjects with CAH.
- To evaluate the pharmacokinetics (PK) of NBI-74788 and metabolites in pediatric subjects with CAH.

Methodology: This is a Phase 2, open-label, multiple-dose study to assess the safety, tolerability, PK, and PD of NBI-74788 in approximately 12 pediatric female and male subjects (14 to 17 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH. NBI-74788 50 mg twice daily (bid) will be administered for 14 consecutive days with breakfast and evening meals beginning on the evening of Day 1.

Parental or legal guardian informed consent with signed and witnessed study subject assent will be obtained prior to any study-related procedures. Subjects will then be screened for up to approximately 3 weeks (Days -28 to -8) for eligibility to participate in the study. During screening, subjects will provide a blood sample in the morning between 0700 and 1000 hours (prior to first morning dose of hydrocortisone) to determine their 17-hydroxyprogesterone (17-OHP) levels for study entry.

Eligible subjects who have a screening 17-OHP level ≥800 ng/dL will be admitted to the study center on Day -7 for 1 night and have baseline serial PD samples collected over a 24-hour period beginning that evening. Baseline serial PD samples will be collected at approximately 1845, 2000, 2300, 0100, 0300, 0700, 1000, 1500, and 1900 hours.

The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

Subjects will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for [redacted]. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. The first dose of study drug, NBI-74788 50 mg, will be administered at approximately 1900 hours with subjects' evening meal on Day 1. Study drug will be administered at the study center on Days 2 and 14 with subjects' breakfast and evening meals, respectively. The subjects' usual morning dose of concurrent steroidal treatments, study drug dosing, and breakfast (snacks will be allowed prior to breakfast) will be delayed until after the 15-hour postdose PD samples are collected (ie, at approximately 1000 hours) on Day 2. The subjects' usual morning dose of concurrent steroidal treatments will be administered after the 15-hour postdose PD samples are collected (ie, at approximately 1000 hours) on Day 15. Subjects will be discharged from the study center in the evening on Days 2 and 15 following completion of all study-related procedures for those days. Study drug will be self-administered at home under parent/guardian supervision at approximately 0700 hours (with breakfast) and 1900 hours (with evening meal) on Days 3 to 13.

On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center.

Follow-up visits on Days 17 and 21 will be conducted at the study center or by a qualified home healthcare provider at the subject's home (based on the subject's preference). A final study visit will be conducted at the study center approximately 3 weeks after the last dose of study drug (on Day 35 or early termination). There will be a visit window of -8 hours for Day 7, -8 hours/+3 days for Days 17 and 21, and +7 days for the final study visit (Day 35 or early termination). Safety, tolerability, PK, and PD will be assessed at scheduled times throughout the study.

Study Population: Approximately 12 pediatric female and male subjects (14 to 17 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH, who meet all protocol eligibility criteria, will be enrolled.

Duration of treatment: The expected duration of study participation for each subject is approximately 9 weeks, including up to approximately 3 weeks for screening, a 24-hour PD baseline period (approximately 7 days prior to the first day of dosing), 14 days of dosing, and a follow-up period of approximately 3 weeks.

Test product, dose, and mode of administration: NBI-74788 will be supplied as capsules containing 50 mg of NBI-74788 [redacted] for oral administration. One capsule of study drug will be administered orally at approximately 0700 hours with breakfast and at approximately 1900 hours with evening meal.

Reference therapy, dose, and mode of administration: Not applicable.

Criteria for evaluation

Pharmacokinetics:

Blood samples for PK analysis will be collected at the following times:

- Days 1 and 14: 15 minutes pre-evening dose and at 1, 4, and 6 hours post-evening dose (±5 minute window).
- Days 2 and 15: 8, 12, and 24 hours post-evening dose (±15 minute window; 24-hour post-evening dose blood sample on Day 15 only).
- Day 7: 12 hours (±2 hour window) after the Day 6 evening dose, prior to the Day 7 morning dose.
- Days 17 and 21: 72 hours (-8 hours/+3 days) and 168 hours (-8 hours/+3 days) post-final dose.
- Final study visit (+7 days; Day 35 or early termination).

The following plasma PK parameters will be calculated for NBI-74788 and metabolites for the Day 1 to 2 and the Day 14 to 15 sampling intervals:

- Area under the plasma concentration versus time curve from 0 to 12 hours ($AUC_{0–12}$).
- Observed maximum plasma concentration (C_{max}).
- Time to C_{max} (t_{max}).

Additional PK parameters for Days 14 to 15 only:

- Average plasma concentration at steady state (C_{avg}).
- Percent fluctuation at steady state (%fluctuation).
- Accumulation ratio at steady state.
- Apparent terminal half-life ($t_{½}$).
- Apparent terminal rate constant (λz).
- Apparent mean residence time (MRT).
- Apparent systemic clearance after oral administration (CL/F) (NBI-74788 only).

Pharmacodynamics:

Blood samples for PD parameters will be collected at the following times:

- Screening (must be collected prior to first morning dose of hydrocortisone).

- Day -7 to Day -6 (24-hour PD baseline): at approximately 1845, 2000, 2300, 0100, 0300, 0700, 1000, 1500, and 1900 hours.
- Days 1 and 14: 15 minutes pre-evening dose and at 1, 4, and 6 hours post-evening dose (±5 minute window).
- Days 2 and 15: 8, 12, 15, 20, and 24 hours post-evening dose (±15 minute window).
- Day 7: 12 hours (±2 hour window) after the Day 6 evening dose and prior to the Day 7 morning dose.
- Day 21: 168 hours (-8 hours/+3 days) following last dose.

[redacted] Morning 17-OHP (serum; ng/dL) from the 8- and 12-hour postdose samples (collected at 0300 and 0700 hours).

[redacted] 17-OHP at all other times, androstenedione (serum; ng/dL), testosterone (serum; ng/dL), cortisol (serum; µg/dL), and adrenocorticotropic hormone (ACTH; plasma; pg/mL).

Safety: Safety and tolerability will be monitored throughout the study and will include the following assessments:

- Treatment-emergent adverse events.
- Clinical laboratory tests (clinical chemistry, hematology, [redacted] and urinalysis).
- Vital signs.
- Physical examinations (including musculoskeletal exam).
- 12-lead electrocardiograms (ECGs).
- Columbia-Suicide Severity Rating Scale (C-SSRS), Children's Version
- Brief Psychiatric Rating Scale for Children (BPRS-C).

Statistical methods: Safety, PK, and PD data will be summarized using descriptive statistics. Summaries of safety measures will include both observed values and changes from baseline. Summaries of PD measures will include both observed values and changes from timepoint-matched PD baseline values.

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

17-OHP	17-hydroxyprogesterone
ACTH	adrenocorticotropic hormone
AE	adverse event
ALT	alanine aminotransferase
[redacted]	[redacted]
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
β-hCG	β-human chorionic gonadotropin
bid	twice daily
BPRS-C	Brief Psychiatric Rating Scale for Children
CAH	congenital adrenal hyperplasia
CFR	Code of Federal Regulations
CK	creatine kinase
C_{max}	observed maximum plasma concentration
CRF1	corticotropin releasing factor 1
C-SSRS	Columbia-Suicide Severity Rating Scale
[redacted]	[redacted]
DSM	Diagnostic and Statistical Manual of Mental Disorders
DSPV	Drug Safety and Pharmacovigilance
ECG	electrocardiogram
eCRF	electronic case report form
EDC	electronic data capture
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase
HbsAg	hepatitis B surface antigen
HCV-Ab	hepatitis C antibody
HIV-Ab	human immunodeficiency virus antibody
ICF	informed consent form
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
[redacted]	[redacted]
IRB	institutional review board

MedDRA	Medical Dictionary for Regulatory Activities
NBI	Neurocrine Biosciences, Inc.
NOAEL	no observed adverse effect level
PD	pharmacodynamics
P-gp	P-glycoprotein
PK	pharmacokinetics
QTcF	QT interval corrected for heart rate using Fridericia's correction
SAE	serious adverse event
SAP	statistical analysis plan
$t_{½}$	apparent terminal half-life
TEAE	treatment-emergent adverse event
t_{max}	time to reach observed maximum plasma concentration
ULN	upper limit of normal
US	United States
WBC	white blood cell

3. ETHICS

The study will be conducted in accordance with Neurocrine Biosciences, Inc. (NBI) standards that meet regulations relating to Good Clinical Practice (GCP). These standards respect the following guidelines:

- GCP: Consolidated Guideline (International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use [ICH; current version]).
- United States (US) Code of Federal Regulations (CFR) dealing with clinical studies (21 CFR parts 50, 54, 56, 312, and 314).
- Canada Food and Drugs Act and Regulations Part C, Division 5: Drugs for Clinical Trials Involving Human Subjects.
- Guidance for Clinical Trial Sponsors: Clinical Trial Applications, Effective March 2016, Health Canada Therapeutic Products Directorate, Health Products and Food Branch.

The ethical requirements of Institutional Review Boards (IRBs)/Ethics Committees and the informed consent forms (ICFs) are discussed in Section 13.

4. INTRODUCTION

4.1. Background

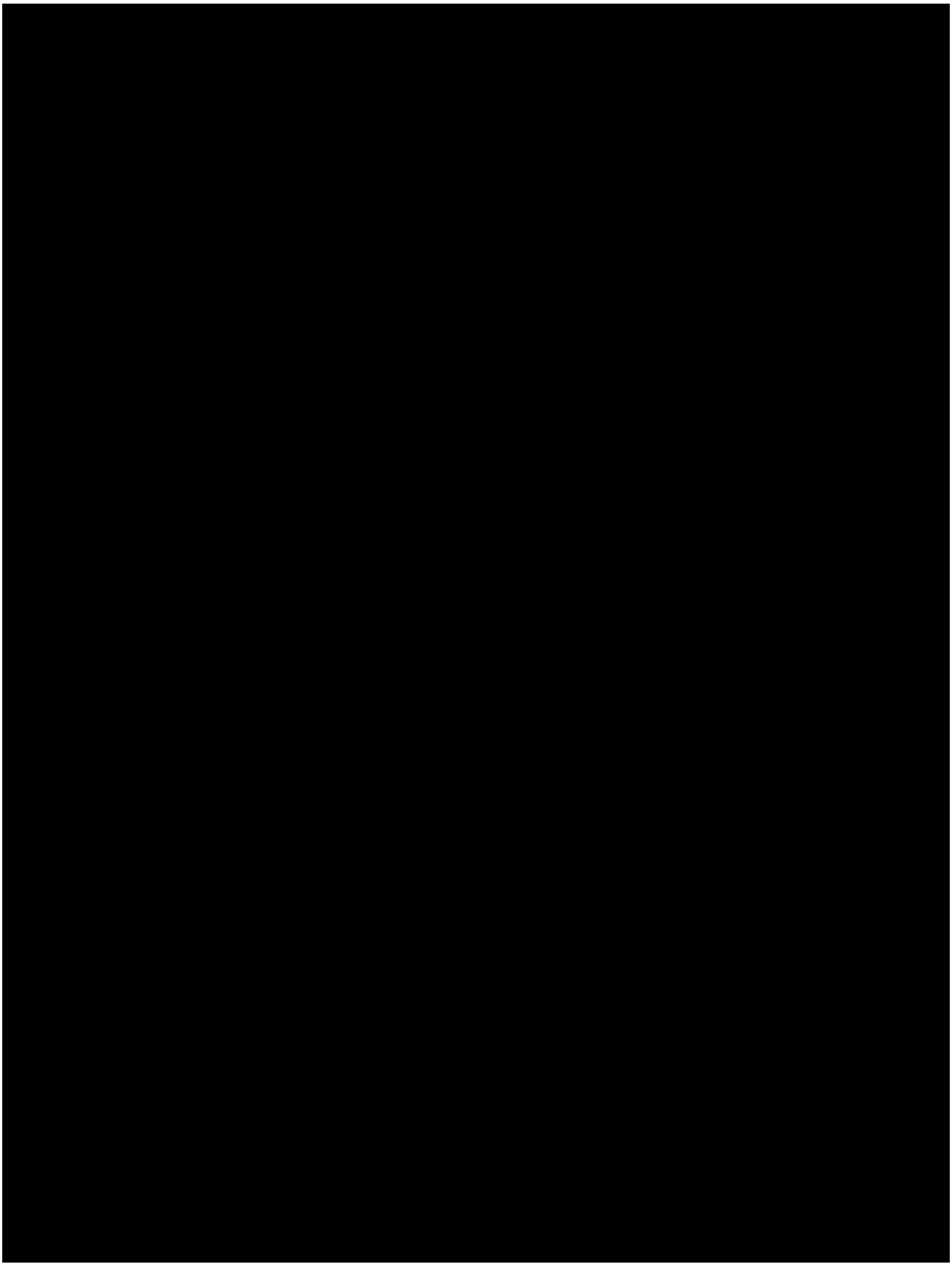
NBI-74788 is a selective corticotropin releasing factor 1 (CRF1) receptor antagonist that is being developed by NBI as a novel oral treatment for classic congenital adrenal hyperplasia (CAH) due to 21-hydroxylase deficiency, a condition that results in little or no cortisol biosynthesis. One clinical manifestation of the absence of cortisol is the lack of feedback inhibition of pituitary adrenocorticotropic hormone (ACTH) secretion. Increased ACTH levels cause adrenal hyperplasia and the enzyme mutation causes a shunting of cortisol precursor steroids to alternate pathways. Most notably, the shunting of androgens leads to virilization and other developmental complications in females and the over-accumulation of ACTH is associated with the formation of testicular adrenal rest tumors in males. In addition, since the same enzyme (21-hydroxylase) is used in the pathway for the biosynthesis of the mineralocorticoids, a number of these patients suffer from aldosterone deficiency which can result in dehydration and death due to salt-wasting. The prevalence of classic 21-hydroxylase deficiency CAH in the US general population, based on newborn screening, has been documented as 1:10,000 to 1:20,800 (Trakakis et al., 2010; Hertzberg et al., 2011), a figure that supports orphan drug designation.

Pediatric patients from birth through adolescence, and females in particular, appear to be the most vulnerable population of CAH sufferers and represent the subgroup of patients with the greatest unmet medical need (Cheng and Speiser, 2012; Merke and Poppas, 2013). Excessive androgen production in these younger patients results in early onset puberty and adrenarche, changes in skeletal maturation patterns, short stature caused by premature growth plate fusion, as well as significant hirsutism and acne problems. While survival is properly ensured through steroid replacement strategies based on physiologic dosing of glucocorticoids (eg, hydrocortisone) and mineralocorticoids (eg, fludrocortisone), these doses are often inadequate to suppress the accumulating ACTH and overproduction of progestogens and

androgens (eg, 17-hydroxyprogesterone [17-OHP], androstenedione, and testosterone). The uncontrolled symptoms of androgen excess, indeed, have a substantial impact on the day-to-day functioning and development of these patients. The glucocorticoid doses required to treat the androgen excess are typically well above the normal physiologic dose used for cortisol replacement alone (as in patients with Addison's disease). This increased exposure to glucocorticoids can lead to iatrogenic Cushing's syndrome, increased cardiovascular risk factors, glucose intolerance, reduced growth velocity, and decreased bone mineral density in CAH patients (Elnecave et al., 2008; King et al., 2006; Migeon and Wisniewski, 2001).

Corticotropin releasing factor is a hypothalamic hormone released directly into the hypophyseal portal vasculature and acts on specific CRF1 receptors on corticotropes in the anterior pituitary to stimulate the release of ACTH. Blockade of these receptors has been shown to decrease the release of ACTH in both animals and humans. Therefore, compounds that block CRF1 receptors have the potential to directly inhibit the excessive ACTH release that occurs in CAH and thereby allow for normalization of androgen production while using lower, more physiologic doses of hydrocortisone. The novel CRF1 receptor antagonist, NBI-74788, may provide an important therapeutic approach to treat patients with CAH.

4.2. NBI-74788



[redacted]

4.3. Study and Dose Rationale

The present Phase 2 study is designed to evaluate the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of NBI-74788 in pediatric subjects 14 to 17 years of age with classic CAH following multiple days of dosing twice daily 50 mg. [redacted]

5. OBJECTIVES

The objectives of the study are as follows:

- To assess the safety and tolerability of NBI-74788 in pediatric subjects 14 to 17 years of age with CAH.
- To evaluate the effect of repeated doses of NBI-74788 on endogenous levels of PD biomarkers in pediatric subjects with CAH.
- To evaluate the PK of NBI-74788 and metabolites in pediatric subjects with CAH.

6. STUDY DESIGN

This is a Phase 2, open-label, multiple-dose study to assess the safety, tolerability, PK, and PD of NBI-74788 in approximately 12 pediatric female and male subjects (14 to 17 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH. NBI-74788 50 mg bid will be administered for 14 consecutive days with breakfast and evening meals beginning on the evening of Day 1.

Parental or legal guardian informed consent with signed and witnessed study subject assent will be obtained prior to any study-related procedures. Subjects will then be screened for up to approximately 3 weeks (Days -28 to -8) for eligibility to participate in the study. During

screening, subjects will provide a blood sample in the morning between 0700 and 1000 hours (prior to first morning dose of hydrocortisone) to determine their 17-OHP levels for study entry.

Eligible subjects who have a screening 17-OHP level ≥800 ng/dL will be admitted to the study center on Day -7 for 1 night and have baseline serial PD samples collected over a 24-hour period beginning that evening. Baseline serial PD samples will be collected at approximately 1845, 2000, 2300, 0100, 0300, 0700, 1000, 1500, and 1900 hours.

The subjects' usual morning dose of steroidal treatments will be administered after the 1000 hours PD sample is collected on Day -6. Subjects will be discharged on Day -6 after the last PD sample is collected.

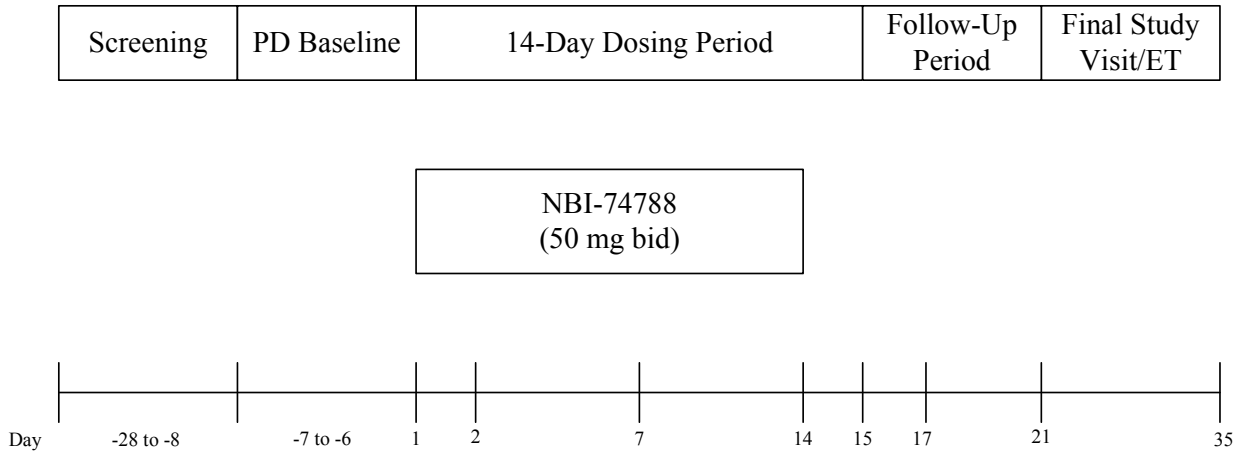
Subjects will be admitted to the study center on Days 1 and 14 (first and last day of dosing). Subjects will have a blood sample collected on Day 1 for [redacted]. Baseline safety assessments will be collected on Day 1 prior to the first dose of study drug. The first dose of study drug, NBI-74788 50 mg, will be administered at approximately 1900 hours with subjects' evening meal on Day 1. Study drug will be administered at the study center on Days 2 and 14 with subjects' breakfast and evening meals, respectively. The subjects' usual morning dose of concurrent steroidal treatments, study drug dosing, and breakfast (snacks will be allowed prior to breakfast) will be delayed until after the 15-hour postdose PD samples are collected (ie, at approximately 1000 hours) on Day 2. The subjects' usual morning dose of concurrent steroidal treatments will be administered after the 15-hour postdose PD samples are collected (ie, at approximately 1000 hours) on Day 15. Subjects will be discharged from the study center in the evening on Days 2 and 15 following completion of all study-related procedures for those days. Study drug will be self-administered at home under parent/guardian supervision at approximately 0700 hours (with breakfast) and 1900 hours (with evening meal) on Days 3 to 13.

On Day 7 during the treatment period, PK, PD, and safety assessments will be conducted in an outpatient setting at the study center.

Follow-up visits on Days 17 and 21 will be conducted at the study center or by a qualified home healthcare provider at the subject's home (based on the subject's preference). A final study visit will be conducted at the study center approximately 3 weeks after the last dose of study drug (on Day 35 or early termination). There will be a visit window of -8 hours for Day 7, -8 hours/+3 days for Days 17 and 21, and +7 days for the final study visit (Day 35 or early termination). Safety, tolerability, PK, and PD will be assessed at scheduled times throughout the study.

The study design schematic is shown in Figure 1. A schematic of study drug dosing and blood draw timepoints is shown in Table 1.

Figure 1: Study Design Schematic



bid=twice daily; ET=early termination; PD=pharmacodynamic.

Table 1: Study Drug Dosing and Blood Draw Timepoints Schematic

Screening	PD Baseline (Day -7)	PD Baseline (Day -6)	Day 1	Day 2	Day 3 – Day 6	Day 7	Day 8 – Day 13	Day 14	Day 15	Day 17	Day 21	Day 35
		PD: 0100, 0300, 0700 hr		PK/PD: 8, 12 hr post		PK/PD: Predose			PK/PD: 8, 12 hr post			
AM DOSING				1000 hr Delayed Dosing with Meal	0700 hr	0700 hr	0700 hr	0700 hr				
PD/Labs: 0700 – 1000 hr (+ [redacted] & Serology)		PD: 1000, 1500, 1900 hr	PK/PD/Labs: Predose + [redacted]	PD: 15, 20, 24 hr post				PK/PD: Predose	PD: 15, 20 hr post PK/PD/Labs: 24 hr post	PK: 72 hr post	PK/PD: 168 hr post	PK/Labs: 504 hr post
PM DOSING			1900 hr	1900 hr	1900 hr	1900 hr	1900 hr	1900 hr				
	PD: 1845, 2000, 2300 hr		PK/PD: 1, 4, 6 hr post					PK/PD: 1, 4, 6 hr post				

[redacted] PD=pharmacodynamic; PK=pharmacokinetic.
Note: blood draws (pre- and post-dose) are relative to evening dosing.

7. STUDY POPULATION

This study will be conducted in approximately 12 pediatric female and male subjects (14 to 17 years of age) with a documented medical diagnosis of classic 21-hydroxylase deficiency CAH. Subjects must meet all inclusion criteria and no exclusion criteria in order to be enrolled.

7.1. Subject Inclusion Criteria

To participate in this study, subjects must meet the following criteria:

1. Have documentation of informed consent by the subject's parent(s) or legal guardian, and of assent by the study subject.
2. Be female or male between 14 to 17 years of age (inclusive).
3. Have a body weight (in kg) greater than or equal to the 10th percentile of his/her age- and gender-matched weight percentile at screening.
4. Be in good general health, as determined by medical history, physical examination, clinical laboratory assessments, and 12-lead ECG.
5. Have a medically confirmed diagnosis of classic 21-hydroxylase deficiency CAH that includes a serum 17-OHP level of ≥800 ng/dL at screening. A medically confirmed diagnosis will be satisfied if the subject is able to provide a medical record of the CAH diagnosis or the investigator can confirm the CAH diagnosis.
6. Have a serum cortisol concentration <5 µg/dL and plasma ACTH concentration ≥20 pg/mL at screening, consistent with the classic 21-hydroxylase deficiency CAH diagnosis.
7. Be on a stable regimen of steroidal treatment for CAH [redacted] that is expected to remain stable throughout the study. [redacted]
8. Subjects of childbearing potential must agree to use contraception consistently from screening until 30 days (females) or 90 days (males) after the last dose of study drug. A female subject of childbearing potential is defined as a female capable of becoming pregnant, which includes subjects who have had their first menstrual cycle (ie, menarche) and are not surgically sterile (ie, bilateral oophorectomy, hysterectomy or bilateral tubal ligation for at least 3 months prior to screening). A male subject of childbearing potential is defined as a subject who has reached spermarche and has not been vasectomized for at least 3 months prior to screening.

[redacted]

[redacted]

9. Female subjects of childbearing potential must have a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test at screening and negative urine pregnancy test at Day 1 (baseline).
10. Subjects must have a negative urine drug screen (negative for amphetamines, barbiturates, benzodiazepine, phencyclidine, cocaine, opiates, or cannabinoids) and negative alcohol breath test at screening, at the start of the 24-hour PD baseline period (Day -7), and on Day 1 (Day -7 and Day 1 eligibility based on urine drug screen and alcohol breath test conducted at the site). Subjects with a positive urine drug screen due to a stable medication regimen to treat a medical condition may participate in the study.
11. Be willing and able to adhere to the study regimen and study procedures described in the protocol and informed consent/assent forms, including all requirements at the study center and return for the follow-up visits.

7.2. Subject Exclusion Criteria

Subjects will be excluded from the study if they:

1. Are currently pregnant or lactating.
2. Are unable to swallow the study drug capsule.
3. Have a clinically significant unstable medical condition or chronic disease (including history of neurological, hepatic, renal, cardiovascular, gastrointestinal, pulmonary, psychiatric or endocrine disease [excluding CAH]), or malignancy that could confound interpretation of study outcome.
4. Had a clinically significant illness within 30 days of screening.
5. Have a known or suspected differential diagnosis of any of the other known classic forms of CAH including [redacted]
6. Have a history that includes bilateral adrenalectomy, hypopituitarism, or other condition requiring daily therapy with orally administered glucocorticoids (eg, asthma, arthritis, or systemic lupus erythematosus).
7. Have any clinically significant acute or unstable chronic abnormal finding in physical examination, neurological assessment, vital signs, ECGs, or clinical laboratory tests, as determined by the investigator.
8. Have a history of epilepsy or serious head injury (eg, traumatic brain injury or post-concussive syndrome).

9. Have a known history of long QT syndrome or cardiac tachy-arrhythmia.
10. Have a screening or Day 1 (baseline) average ECG QT interval corrected for heart rate using Fridericia's correction (QTcF) of >450 msec or the presence of any clinically significant cardiac abnormality.
11. Have an exaggerated pharmacological sensitivity (ie, hypersensitivity) to any corticotropin releasing hormone (CRH) antagonists.
12. Test positive at screening for hepatitis B surface antigen (HBsAg), hepatitis C antibody (HCV-Ab), or human immunodeficiency virus antibody (HIV-Ab) or have a history of a positive result.

18. Have used any other investigational drug within 30 days or 5 half-lives (whichever is longer) before initial screening or plan to use an investigational drug (other than the study drug) during the study.
19. Currently use any excluded concomitant medication (refer to Section 8.9.1) and cannot discontinue use of these medications for the duration of the study.

20. Have a history of substance (drug or alcohol) dependence or abuse within the 3 months before Day 1 (baseline), as defined in the Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV (Substance Dependence or Abuse) or DSM-5 (Substance Use Disorder).
21. Have ingested foods containing poppy seeds within 7 days before screening, the start of the 24-hour PD baseline period (Day -7), and Day 1.

[redacted]

23. Have had a blood loss ≥250 mL due to a surgical procedure or blood donation within 56 days before Day 1 (baseline).
24. Have a significant risk of suicidal or violent behavior. Subjects will be excluded if they have:
    - Any 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 1 year before screening based on the Columbia-Suicide Severity Rating Scale (C-SSRS) Children's Version.
25. In the investigator's opinion, the subject is not capable of adhering to the protocol requirements.

7.3. Subject Identification and Replacement

Subjects will be identified during the study by a unique subject identification number. The identification number will be written on all source documentation and laboratory specimens and populated on all electronic Case Report Forms (eCRFs). Subjects who discontinue the study due to causes other than TEAEs may be replaced.

7.4. Randomization

This is a single-arm study.

8. STUDY EVALUATIONS

8.1. Schedule of Assessments

Table 2 summarizes the frequency and timing of all study assessments and procedures for the study. Parent(s) or legal guardian(s) will provide informed consent with signed (or verbal, if applicable) and witnessed study subject assent before the performance of any study-related procedures. Subject-related activities and events including specific instructions, procedures, concomitant medications, dispensing of study drug, and descriptions of AEs will be recorded in the appropriate source documents and eCRFs.

Table 2: Schedule of Assessments

Assessment	Screening	PD Baseline	14-Day Dosing Period							Follow-Up Period		Final Study Visit[a]
Study Day	**-28 to -8**	**-7 to -6**	**1[b]**	**2**	**3-6**	**7**	**8-13**	**14**	**15**	**17**	**21**	**35 (+7 days)**
Informed consent and assent	X											
Inclusion/exclusion criteria	X	Update	Update									
Medical history	X	Update	Update									
Physical examination	X		X	X		X			X			X
Height	X											X
Weight	X		X						X			X
Vital signs	X	X	X	X[c]		X		X	X[c]			X
12-lead ECG[d]	X		X	X				X	X			X
Pregnancy test[e]	X(s)	X(u)	X(u)			X(u)			X(u)			X (u)
Serology (HBsAg, HCV-Ab and HIV-Ab)	X											
[redacted]												
Clinical laboratory test[f]	X		X						X			X
[redacted]												
UDS and alcohol breath test[h]	X	X	X					X				
PD blood samples[i]	X	X	X	X		X		X	X		X	
[redacted]												
C-SSRS, Children's Version	X		X						X			X
PK plasma samples[k]			X	X		X		X	X	X	X	X
Study drug dosing[l]			X	X	X	X	X	X				
Subject study diary[m]			X	X	X	X	X	X				
Study drug reconciliation[n]						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	X	X	X
Outpatient visit	X					X[o]				X[p]	X[p]	X
Inpatient center stays		X	X	X				X	X			

Definitions: 17-OHP=17-hydroxyprogesterone; ACTH=adrenocorticotropic hormone; AE=adverse event; [redacted]; C-SSRS=Columbia-Suicide Severity Rating Scale; [redacted] ECG=electrocardiogram; HBsAg=hepatitis B surface antigen; HCV-Ab=hepatitis C virus antibody; HIV-Ab=human immunodeficiency virus antibody; PD=pharmacodynamic; PK=pharmacokinetic; s=serum; u=urine; UDS=urine drug screen.
Footnotes are on the following page.

[a] Final study visit for subjects who complete the study (or early termination). The final study visit will be conducted approximately 3 weeks (+7 days) after the last dose of study drug.
[b] Day 1 occurs 1 week after the Day -7 visit. Day 1 assessments will be collected predose unless otherwise noted below. Safety assessments collected predose on Day 1 will serve as the baseline.
[c] Vital signs will be collected on Days 2 and 15 between 8 and 10 and 22 and 24 hours post-evening dose (ie, morning and evening).
[d] A standard 12-lead ECG will be conducted in triplicate (1 to 3 minutes apart) after subject has rested supine for at least 5 minutes at screening, pre-evening dose on Days 1 and 14, prior to visit completion or discharge on Days 2 and 15, and at the final study visit (Day 35 or early termination).
[e] Pregnancy tests will be conducted for female subjects of childbearing potential. A serum pregnancy test will be conducted at screening, and urine pregnancy tests will be conducted at other timepoints. The pregnancy test will be conducted prior to dosing on Day 1 (for eligibility).
[f] Includes hematology, clinical chemistry (including creatine kinase, myoglobin, total and conjugated bilirubin), and urinalysis (including quantitative myoglobin, casts and crystals). Samples will be obtained under nonfasted conditions.
[redacted]
[h] Urine testing kits will be provided by the central laboratory to confirm negative drug screen prior to Day -7 PD collection and Day 1 dosing. Separate urine sample will also be sent to the central laboratory for analysis.
[i] Blood samples for analyses of 17-OHP, androstenedione, testosterone, cortisol, and ACTH will be collected at the following times:
- Screening (between 0700 and 1000 hours; must be collected prior to first morning dose of hydrocortisone).
- Day -7 to Day -6 (24-hour PD baseline): at approximately 1845, 2000, 2300, 0100, 0300, 0700, 1000, 1500, and 1900 hours.
- Days 1 and 14: 15 minutes pre-evening dose and at 1, 4, and 6 hours post-evening dose (±5 minute window).
- Days 2 and 15: 8, 12, 15, 20, and 24 hours post-evening dose (±15 minute window). The subjects' usual morning dose of concurrent steroidal treatments, study drug dosing, and breakfast (snacks will be allowed prior to breakfast) will be delayed until after the 15 hour postdose PD samples are collected (ie, at approximately 1000 hours) on Day 2. The subjects' usual morning dose of concurrent steroidal treatments will be administered after the 15 hour postdose samples are collected (ie, at approximately 1000 hours) on Day 15.
- Day 7: 12 hours (±2 hour window) after the Day 6 evening dose and prior to the Day 7 morning dose (study drug dosing should not occur until after the blood sample has been collected).
- Day 21: 168 hours (-8 hours/+3 days) following last dose.

[redacted]
[k] Pharmacokinetic plasma samples will be collected at the following times:
- Days 1 and 14: 15 minutes pre-evening dose and at 1, 4, and 6 hours post-evening dose (±5 minute window).
- Days 2 and 15: 8, 12, and 24 hours post-evening dose (±15 minute window; 24-hour post-evening dose blood sample on Day 15 only).
- Day 7: 12 hours (±2 hour window) after the Day 6 evening dose, prior to the Day 7 morning dose (study drug dosing should not occur until after the blood sample has been collected).
- Days 17 and 21: 72 hours (-8 hours/+3 days) and 168 hours (-8 hours/+3 days) post-final dose.
- Final study visit (+7 days; Day 35 or early termination).

[l] The first dose of study drug will be administered at approximately 1900 hours with subjects' evening meal on Day 1. Study drug will be administered at the study center on Days 2 and 14 with subjects' breakfast and evening meals, respectively. The subjects' usual morning dose of concurrent steroidal treatments, study drug dosing, and breakfast (snacks will be allowed prior to breakfast) will be delayed until after the 15-hour postdose PD samples are collected (ie, at approximately 1000 hours) on Day 2. Study drug will be self-administered at home under parent/guardian supervision at approximately 0700 hours (with breakfast) and 1900 hours (with evening meal) on Days 3 to 13.
[m] Subject study diary will be provided to subjects on Day 1 prior to dosing. The date and time of study drug administration, the number of capsules taken, and confirmation that study drug was taken with breakfast and the evening meal will be documented each day. The diary will be reviewed for completeness at the Day 7 visit. The subject will return the diary at the Day 14 visit.
[n] A compliance check will be performed by counting the number of capsules returned.
[o] Sites should call subjects between the Day 2 and Day 7 visits to remind them to complete the subject study diary, check on compliance, and remind them to bring subject study diary and remaining study drug to the Day 7 visit.
[p] Subjects will have the option of having the Days 17 and 21 assessments conducted at home by a qualified home healthcare provider or at the study center.

8.2. Screening and Baseline Assessments

8.2.1. Serum 17-Hydroxyprogesterone

A blood sample will be collected at screening (approximately 7 mL) to measure morning serum 17-OHP (and other PD analytes) between 0700 and 1000 hours (prior to first morning dose of hydrocortisone) to determine subject eligibility. Subjects must have serum 17-OHP level of ≥800 ng/dL at screening to be eligible for study enrollment.

8.2.2. [redacted]

[redacted]

8.3. Pharmacokinetic Assessments

Approximately 2 mL of blood will be collected for each sample. PK samples will be sent to a central laboratory which will provide instructions and supplies to the study staff before study initiation.

For blood sample collection performed while subjects are asleep, every effort should be made to minimize disturbances to the subjects.

PK plasma samples for analyses of NBI-74788 will be collected at the following times:

- Days 1 and 14: 15 minutes pre-evening dose and at 1, 4, and 6 hours post-evening dose (±5 minute window).
- Days 2 and 15: 8, 12, and 24 hours post-evening dose (±15 minute window; 24-hour post-evening dose blood sample on Day 15 only).
- Day 7: 12 hours (±2 hour window) after the Day 6 evening dose, prior to the Day 7 morning dose (study drug dosing should not occur until after the blood sample has been collected).
- Days 17 and 21: 72 hours (-8 hours/+3 days) and 168 hours (-8 hours/+3 days) post-final dose.
- Final study visit (+7 days; Day 35 or early termination).

The exact time of sampling in hour and minutes will be recorded.

The blood samples will be processed to plasma, which will be stored as specified in the laboratory manual. These samples will be shipped on dry ice to the central laboratory for analysis. Refer to the laboratory manual for additional details.

Plasma samples remaining at the end of the study may be used for exploratory assessments of NBI-74788 metabolites.

An in-home service (phlebotomist) will be available for blood draws on Days 17 and 21.

8.4. Pharmacodynamic Assessments: Pharmacodynamic Biomarkers

Approximately 7 mL of blood will be collected for each sample. PD biomarker samples will be sent to a central laboratory which will provide instructions and supplies to the study staff before study initiation.

Blood samples to measure cortisol (serum; µg/dL), 17-OHP (serum; ng/dL), androstenedione (serum; ng/dL), testosterone (serum; ng/dL), and ACTH (plasma; pg/mL) will be collected at:

- Screening (between 0700 and 100 hours; must be collected prior to first morning dose of hydrocortisone).
- Day -7 to Day -6 (24-hour PD baseline): at approximately 1845, 2000, 2300, 0100, 0300, 0700, 1000, 1500, and 1900 hours.
- Days 1 and 14: 15 minutes pre-evening dose and at 1, 4, and 6 hours post-evening dose (±5 minute window).
- Days 2 and 15: 8, 12, 15, 20, and 24 hours post-evening dose (±15 minute window).
- Day 7: 12 hours (±2 hour window) after the Day 6 evening dose and prior to the Day 7 morning dose (study drug dosing should not occur until after the blood sample has been collected).
- Day 21: 168 hours (-8 hours/+3 days) following last dose.

The exact time of sampling in hour and minutes will be recorded.

The blood samples will be processed and stored as specified in the laboratory manual. These samples will be shipped on dry ice to the central laboratory for analysis. Refer to the laboratory manual for additional details.

An in-home service (phlebotomist) will be available for blood draws on Day 21.

8.5. Safety Assessments

Concomitant medication use and AEs will be monitored throughout the study as described in Section 8.9.1 and Section 10, respectively. Additional safety assessments are described in the following sections.

Appropriate psychiatric evaluation and intervention will be provided for any treatment-emergent suicidal behavior or clinically significant suicidal ideation.

For any abnormal safety assessment deemed clinically significant, the investigator will perform appropriate follow-up assessments (eg, repeat analysis), until the cause of the abnormality is determined and/or until the value returns to baseline (or within normal limits), or the investigator deems the abnormality to be of no clinical significance.

8.5.1. Vital Sign Measurements

Vital sign measurements, including orthostatic systolic and diastolic blood pressures, orthostatic heart rate, respiratory rate, and oral body temperature will be conducted. Blood pressure will be measured using a calibrated automatic blood pressure cuff after the subject has been supine for at

least 5 minutes and after approximately 2 minutes of standing. The automatic blood pressure cuff will also provide pulse rate measurement.

As much as possible, vital sign measurements will be collected before scheduled blood sample collection. Vital sign measurements will be collected at the following times:

- Screening.
- Day -7 (PD baseline).
- Day 1.
- Day 2 (between 8 and 10 and 22 and 24 hours post-evening dose [ie, morning and evening]).
- Day 7.
- Day 14.
- Day 15 (between 8 and 10 and 22 and 24 hours post-evening dose [ie, morning and evening]).
- Day 35 (or early termination).

8.5.2. Medical History and Physical Examination

A medical history will be taken at the screening visit and updated on Day -7 and Day 1.

A complete physical examination will be conducted at screening and on Days 1, 2, 7, 15, and 35 (or early termination). The complete physical examination will consist of an assessment of general appearance, skin and mucosae, head, eyes, ears, nose, throat, neck (including thyroid), lymph nodes, chest/lungs, cardiovascular, abdomen, extremities, neurological and musculoskeletal systems. Height and weight will be measured with subjects not wearing shoes. Height will be measured at screening and Day 35 (or early termination). Weight will be measured at screening and on Days 1, 15, and 35 (or early termination).

8.5.3. 12-Lead Electrocardiogram

12-lead ECG will be conducted in triplicate (1 to 3 minutes apart) after the subject has rested supine for at least 5 minutes at the following times:

- Screening.
- Days 1 and 14 (pre-evening dose).
- Days 2 and 15: prior to visit completion or discharge.
- Day 35 (or early termination).

The ECG parameters that will be assessed include heart rate, PR interval, QRS duration, QT interval, and QTcF (machine readings). Additionally, the occurrence of de- and re-polarization and rhythm disorders or other abnormalities will be assessed. Based on the review of these parameters, the investigator or designee will note if the ECG is Normal, Abnormal Not Clinically Significant, or Abnormal Clinically Significant. If the ECG is Abnormal Clinically Significant, the investigator will provide a description of the abnormality recorded on the AE eCRF.

8.5.4. Clinical Laboratory Assessments

All clinical laboratory assessments will be conducted by a central laboratory, which will provide instructions and supplies to the study staff before study initiation. The instructions will be included in a laboratory manual. The laboratory test battery will include routine and screening laboratory tests. Samples will be obtained under nonfasted conditions.

Clinical laboratory assessments will be conducted at the following times:

- Screening.
- Day 1.
- Day 15.
- Day 35 (or early termination; [redacted]).

The following clinical safety laboratory assays will be conducted:

Hematology: complete blood count including WBC count with differential, red blood cell count, hemoglobin, hematocrit, platelet count, mean corpuscular hemoglobin (MCH), mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), red cell distribution width (RDW), mean platelet volume (MPV).

Clinical chemistry: sodium, potassium, calcium, magnesium, chloride, blood urea nitrogen, bicarbonate, creatinine, uric acid, albumin, alkaline phosphatase, lactate dehydrogenase, AST, ALT, gamma-glutamyl transferase (GGT), CK, myoglobin, total and conjugated bilirubin, total cholesterol, triglycerides, total protein, and glucose.

Urinalysis: specific gravity, nitrite, ketones, protein, urobilinogen, glucose, bilirubin, leukocyte esterase, occult blood, pH, and quantitative myoglobin. Microscopic examination of sediment will include evaluation for casts and crystals.

The following additional laboratory tests will be conducted:

[redacted]

Serology: Blood will be collected for HBsAg, HCV-Ab, and HIV-Ab testing at screening.

Urine drug screen and alcohol breath test: The urine drug screen will test for amphetamines barbiturates, phencyclidine, benzodiazepines, cannabinoids, cocaine, and opiates. A urine drug screen and alcohol breath test will be conducted at screening, Day -7, Day 1, and Day 14. Urine testing kits will be provided by the central laboratory to confirm negative drug screen prior to Day -7 PD collection and Day 1 dosing. Separate urine sample will also be sent to the central laboratory for analysis.

Pregnancy test: Pregnancy tests will be conducted for female subjects of childbearing potential. Serum pregnancy tests (β-hCG) will be conducted at screening and urine pregnancy tests will be conducted on Day -7, prior to dosing on Day 1 (for eligibility), Day 7, Day 15, and at the final study visit (Day 35 or early termination).

For any abnormal tests deemed clinically significant, repeat analysis will be conducted until the cause of the abnormality is determined or until the value returns to baseline (or within normal limits), or the investigator deems the abnormality to be of no clinical significance.

8.5.5. Brief Psychiatric Rating Scale for Children

The Brief Psychiatric Rating Scale for Children (BPRS-C) was created to provide a concise profile of childhood behavioral and emotional symptomatology (Hughes et al., 2001; Overall and Pfefferbaum, 1982). The BPRS-C includes 21 items that assess behavioral problems, depression, thinking disturbance, psychomotor excitation, withdrawal, anxiety, and organicity. The severity of each of the 21 items of the BPRS-C is rated on a scale of 0 (not present) to 6 (extremely severe) (total score range: 0 to 126). Higher scores represent greater symptom severity.

[redacted]

8.5.6. Columbia-Suicide Severity Rating Scale Children's Versions

The C-SSRS is a validated instrument to prospectively assess suicidal ideation and behavior (http://www.cssrs.columbia.edu). There are versions of the questionnaire designed for use at screening (Children's Screening/Baseline version) and at visits throughout the study (Children's Since Last Visit version). All versions of the C-SSRS include a series of screening questions related to suicidal ideation and suicidal behavior. Subject responses of 'yes' to one or more screening questions will prompt additional questions that evaluate frequency and intensity of suicidal ideation and/or behavior. Subjects with any 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 past 1 year before screening based on the C-SSRS Children's Version should be excluded (see exclusion criterion #24).

The C-SSRS will be administered and scored by the investigator or other qualified site personnel who completed C-SSRS certification. The C-SSRS will be administered at screening, Day 1, Day 15, and at the final study visit (Day 35 or early termination). The "Children's Screening/Baseline" version of the scale will be used to evaluate subject eligibility at screening and the "Children's Since Last Visit" version will be used at all other times.

8.5.7. Estimated Total Blood Sample Volume Required by Study

The estimated total blood sample volume for each subject for the entire study is presented in Table 3. These estimates include samples to be collected during screening and throughout the study.

Table 3: Estimated Total Blood Sample Volume

Parameter	Number of Samples Required	Approximate Volume (mL)	Approximate Total Volume (mL)
Clinical laboratory[a]	4	7	28
[redacted]	3	4.5	13.5
Serology	1	9	9
[redacted]	1	2	2
Pharmacodynamics	30	7	210
Pharmacokinetics	17	2	34
Approximate Maximum Total Blood Sample Volume per Subject (mL):			**296.5**

[a] Includes clinical chemistry, hematology, and serum pregnancy samples.

8.6. Subject Study Diary

The site will provide each subject with a subject study diary on Day 1 prior to dosing. The date and time of study drug administration, the number of capsules taken, and confirmation that study drug was taken with breakfast and evening meal will be documented each day. The diary will be reviewed for completeness at the Day 7 visit. The subject will return the diary at the Day 14 visit.

8.7. Specific Study Period Information

8.7.1. Screening Period (Study Days -28 to -8)

After obtaining informed consent by the subject's parent(s) or legal guardian, and study subject assent, subjects will undergo screening procedures within 21 days of Day -7.

The following study evaluations and tasks will be performed during screening:

- Assess inclusion/exclusion criteria.
- Collect medical history.
- Perform a physical examination including height and weight.
- Collect vital signs.
- Perform 12-lead ECG in triplicate (1 to 3 minutes apart).
- Perform a serum pregnancy test (β-hCG) for female subjects of childbearing potential.
- Collect blood sample for serology testing (HIV-Ab, HBsAg, and HCV-Ab).
- Collect blood sample for clinical laboratory and [redacted] parameters.
- Collect urine sample for urinalysis.
- Collect urine for drug screen (central laboratory) and perform alcohol breath test.

- Collect blood sample for PD biomarkers between 0700 and 1000 hours (prior to first morning dose of hydrocortisone). Subject must have serum 17-OHP level ≥800 ng/dL to be enrolled in the study.
- Administer the C-SSRS (Children's Screening/Baseline version).
- AE monitoring.
- Record prior and concomitant medications.

Eligible subjects will be instructed to return to the study center on Day -7.

8.7.2. Day -7 to Day -6: 24-Hour Baseline Pharmacodynamics

Subjects who continue to meet eligibility requirements will return to the study center for a 24-hour in-patient stay, during which blood samples will be collected for PD analysis. Subjects will not take their usual morning dose of steroidal treatment until after the 1000 hours PD sample is collected on Day -6.

The following study evaluations and tasks will be performed on Day -7 to Day -6:

- Update inclusion/exclusion criteria and medical history.
- Collect vital signs.
- Perform a urine pregnancy test (β-hCG) for female subjects of childbearing potential.
- Collect urine for drug screen and perform alcohol breath test. Urine testing kits will be provided by the central laboratory to confirm negative drug screen prior to PD collection. A separate urine sample will also be sent to the central laboratory for analysis.
- Collect blood samples for PD biomarkers at approximately 1845, 2000, 2300, 0100, 0300, 0700, 1000, 1500, and 1900 hours.
- AE monitoring.
- Record prior and concomitant medications.

Eligible subjects will be instructed to return to the study center on Day 1.

8.7.3. Treatment Period

The study will consist of a 14-day treatment period and will include 2 overnight in-patient stays (on Day 1 to Day 2 and Day 14 to Day 15) and a study center visit on Day 7.

8.7.3.1. Day 1 to Day 2

Subjects will be admitted to the study center on Day 1 and will be discharged in the evening of Day 2 after the 24-hour postdose procedures have been performed. Standard meals and snacks will be provided during the in-patient stay. The procedures to be conducted on these days are described in the following sections.

Day 1

Subjects will report to the study center on Day 1. The following study evaluations and tasks will be performed prior to dosing on Day 1:

- Update inclusion/exclusion criteria and medical history.
- Perform a physical examination including weight.
- Collect vital signs.
- Perform 12-lead ECG in triplicate (1 to 3 minutes apart).
- Perform a urine pregnancy test (β-hCG) for female subjects of childbearing potential.
- [redacted]
- Collect blood sample for clinical laboratory and [redacted] parameters.
- Collect urine sample for urinalysis.
- Collect urine for drug screen and perform alcohol breath test. Urine testing kits will be provided by the central laboratory to confirm negative drug screen prior to dosing. A separate urine sample will also be sent to the central laboratory for analysis.
- Collect blood sample for PD biomarkers at 15 minutes predose (±5 minute window).
- Collect blood sample for PK at 15 minutes predose (±5 minute window).
- [redacted]
- Administer the C-SSRS (Children's Since Last Visit version).
- AE monitoring.
- Record prior and concomitant medications.
- Provide subject with a subject study diary and instruct him/her to document in the diary the date and time of study drug administration, the number of capsules taken, and confirmation that study drug was taken with breakfast and evening meal each day.

At approximately 1900 hours, each subject will receive study drug with the evening meal as described in Section 9.3.

The following study evaluations and tasks will be performed after dosing on Day 1 while the subject remains in bed (as applicable):

- Collect blood samples for PD biomarkers at 1, 4, and 6 hours postdose (±5 minute window).
- Collect blood samples for PK at 1, 4, and 6 hours postdose (±5 minute window).
- AE monitoring.
- Record concomitant medications.

Day 2

The subjects' usual morning dose of concurrent steroidal treatments, study drug dosing, and breakfast (snacks will be allowed prior to breakfast) will be delayed until after the 15 hour postdose PD samples are collected (ie, at approximately 1000 hours).

The following study evaluations and tasks will be performed on Day 2:

- Perform a physical examination.
- Collect vital signs between 8 and 10 and 22 and 24 hours post-evening dose (ie, morning and evening).
- Perform 12-lead ECG in triplicate (1 to 3 minutes apart) predose.
- Collect blood samples for PD biomarkers at 8, 12, 15, 20, and 24 hours post-evening dose (±15 minute window).
- Collect blood samples for PK at 8 and 12 hours post-evening dose (±15 minute window).
- [redacted]
- AE monitoring.
- Record concomitant medications.

The following procedures will be conducted *before* subjects may be discharged from the study center:

- At approximately 1900 hours, each subject will receive study drug with their evening meal as described in Section 9.3.
- Instruct male subjects and female subjects of childbearing potential who do not practice total abstinence to continue using contraception.
- Instruct subjects to notify the investigator or study staff by telephone if they experience any AEs and before taking any concomitant medications.
- Instruct subjects to continue taking study drug with breakfast (approximately 0700 hours) and with their evening meal (approximately 1900 hours) through Day 13 as described in Section 9.3, and to document in the diary the date and time of study drug administration, the number of capsules taken, and confirmation that study drug was taken with breakfast and the evening meal each day.
- Instruct subjects to bring the subject study diary as well as the remaining study drug back for the Day 7 visit.

Sites should call subjects between the Day 2 and Day 7 visits to remind them to complete the subject study diary, check on compliance, and remind them to bring subject study diary and remaining study drug to the Day 7 visit.

8.7.3.2. Day 7

The following procedures will be performed at the study center on Day 7:

- Perform a physical examination.
- Collect vital signs.
- Perform a urine pregnancy test (β-hCG) for female subjects of childbearing potential.
- Collect blood samples for PD biomarkers at approximately 12 hours (±2 hour window) after the Day 6 evening dose and prior to the Day 7 morning dose.
- Collect blood samples for PK at approximately 12 hours (±2 hour window) after the Day 6 evening dose and prior to the Day 7 morning dose.
- Check subject study diary.
- Study drug reconciliation.
- AE monitoring.
- Record concomitant medications.

The following additional procedures will be conducted on Day 7:

- Instruct subjects to perform study drug dosing (as described in Section 9.3) and subject study diary entry at home.
- Instruct subjects to return to the study center on Day 14 before evening dosing and to bring their study drug bottle including any unused study drug, and their subject study diary.

8.7.3.3. Day 14 to Day 15

Subjects will return to the study center on Day 14 and will be discharged in the evening of Day 15 after the 24-hour postdose procedures have been performed. Standard meals and snacks will be provided. The procedures to be conducted on these days are described in the following sections.

Day 14

Subjects will return to the study center on Day 14. The following study evaluations and tasks will be performed prior to evening dosing on Day 14:

- Collect vital signs.
- Perform 12-lead ECG in triplicate (1 to 3 minutes apart).
- Collect blood sample for PD biomarkers at 15 minutes predose (±5 minute window).
- Collect blood sample for PK at 15 minutes predose (±5 minute window).
- Collect urine for drug screen and perform alcohol breath test.
- [redacted]
- Collect the study drug bottle including any unused study drug.

- Study drug reconciliation.
- AE monitoring.
- Record concomitant medications.

At approximately 1900 hours, each subject will receive study drug with their evening meal as described in Section 9.3. After study drug dosing, subjects will record in the subject study diary the date and time of study drug administration, the number of capsules taken, and confirmation that study drug was taken with the evening meal. The subject study diary will then be collected. Subjects will then go to bed.

The following procedures will be conducted after evening dosing on Day 14 while the subject remains in bed (as applicable):

- Collect blood samples for PD biomarkers at 1, 4, and 6 hours post-evening dose (±5 minute window).
- Collect blood samples for PK at 1, 4, and 6 hours post-evening dose (±5 minute window).
- AE monitoring.
- Record concomitant medications.

Day 15

The subjects' usual morning dose of concurrent steroidal treatments will be administered after the 15 hour postdose PD samples are collected (ie, at approximately 1000 hours) on Day 15.

The following procedures will be performed on Day 15:

- Perform a physical examination including weight.
- Collect vital signs between 8 and 10 and 22 and 24 hours post-evening dose (ie, morning and evening).
- Perform 12-lead ECG in triplicate (1 to 3 minutes apart).
- Perform a urine pregnancy test (β-hCG) for female subjects of childbearing potential.
- Collect blood sample for clinical laboratory and [redacted] parameters.
- Collect urine sample for urinalysis.
- Collect blood samples for PD biomarkers at 8, 12, 15, 20, and 24 hours post-evening dose (±15 minute window).
- Collect blood samples for PK at 8, 12, and 24 hours post-evening dose (±15 minute window).
- [redacted]
- Administer the C-SSRS (Children's Since Last Visit version).
- AE monitoring.
- Record concomitant medications.

The following procedures will be conducted before subjects may be discharged from the study center:

- Instruct male subjects and female subjects of childbearing potential who do not practice total abstinence to continue using contraception.
- Instruct subjects to notify the investigator or study staff by telephone if they experience any AEs and before taking any concomitant medications.
- Confirm if the subject prefers to have the Days 17 and 21 visits conducted at home instead of at the study center.
  - If the subject elects to have a home visit, instruct him/her that the qualified home healthcare provider will contact him/her to schedule the visit.
  - If the subject elects to come into the study center, instruct him/her to return on Days 17 and 21.

8.7.4. Follow-Up Period

Follow-up visits will be conducted on Days 17 and 21 with a final study visit on Day 35 (or early termination). Based on their preference, the subject will either come into the study center, or the qualified home healthcare provider will come to the subject's home on Days 17 and 21. The final study visit will be conducted at the study center.

8.7.4.1. Follow-Up Visits: Days 17 and 21

The following procedures will be performed on Days 17 and 21 (-8 hours/+3 days):

- Collect blood sample for PD biomarkers at approximately 168 hours (-8 hours/+3 days; Day 21 only) following the last dose.
- Collect blood samples for PK at approximately 72 hours (-8 hours/+3 days) and 168 hours (-8 hours/+3 days) following the last dose.
- AE monitoring.
- Record concomitant medications.

At each visit, subjects will be reminded to notify the investigator or study staff by telephone if they experience any AEs and before taking any concomitant medications.

At the Day 21 visit, subjects will be reminded to report to the study center on Day 35 (+7 days) for the final study visit (or at early termination).

8.7.4.2. Final Study Visit: (Day 35 or Early Termination)

Subjects will return to the study center for the final study visit (Day 35 or early termination [+7 days]).

The following procedures will be conducted at the final study visit:

- Perform a physical examination including height and weight.

- Collect vital signs.
- Perform 12-lead ECG in triplicate (1 to 3 minutes apart).
- Perform a urine pregnancy test (β-hCG) for female subjects of childbearing potential.
- Collect blood sample for clinical laboratory parameters.
- Collect urine sample for urinalysis.
- Collect blood sample for PK.
- [redacted]
- Administer the C-SSRS (Children's Since Last Visit version).
- AE monitoring.
- Record concomitant medications.

8.8. Study Duration

The expected duration of study participation for each subject is approximately 9 weeks, including up to approximately 3 weeks for screening, a 24-hour PD baseline period (approximately 7 days prior to the first day of dosing), 14 days of dosing, and a follow-up period of approximately 3 weeks.

8.9. Prohibitions and Restrictions

8.9.1. Prior and Concomitant Medications

All prescription and over-the-counter medications, dietary supplements (including vitamins), and herbal supplements taken by the subject during the 30 days before screening will be recorded on the Prior and Concomitant Medications page of the eCRF.

Subjects must be on a stable regimen of steroidal treatment for CAH for a minimum of 30 days before PD baseline (Day -7) and the regimen should remain stable throughout the study. [redacted] Female subjects of childbearing potential may use hormonal contraception during the study if taken for at least 3 months prior to screening. Subjects who are on stable medication regimens to treat stable medical conditions (other than CAH) are allowed to participate in the study.

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

- Orally administered glucocorticoids for indications other than CAH.

[redacted]

- As-needed doses of anxiolytics.

Any concomitant medication taken during the study will be recorded on the Prior and Concomitant Medications page of the eCRF with indication, total daily dose, route, and dates of drug administration.

Any additions, deletions, or changes in the dose of medications during the study should be recorded on the appropriate eCRF page.

8.9.2. Dietary and Other Restrictions

Subjects may be confined to the study center for approximately 24 hours three times during the study: on Days -7 to -6 (for PD baseline sample collection), Days 1 to 2, and Days 14 to 15. In these instances, subjects will be discharged from the study center after completion of the required procedures.

Foods containing poppy seeds are prohibited from 7 days before screening until the final study visit.

Strenuous activity beyond what is customary for the subject is prohibited during the study.

Subjects must not donate blood or blood products from 30 days before Day -7 until 30 days after the final study visit (or early termination). Male subjects must agree to refrain from donating sperm for 90 days after the last dose of study drug.

Participation in another investigational drug study is prohibited for at least 30 days after the last dose of study drug in the current study.

8.10. Withdrawal Criteria

8.10.1. Reasons for Withdrawal

Subjects are free to discontinue their participation in the study at any time. The investigator must withdraw any subject from the study if that subject requests to be withdrawn.

The investigator must withdraw the subject from the study if the subject experiences any of the following:

- If the type, frequency, or severity of any AE becomes unacceptable/intolerable.
- QTcF value >500 msec (one or more value; cardiologist verified).
- Is lost to follow up.
- Subject is confirmed to be pregnant.

The investigator or NBI may withdraw the subject from the study for other reasons as described below.

- Develops an ECG abnormality.
- Liver function test values for AST or ALT exceed 2.5 times ULN, GGT exceeds 3 times ULN, or total bilirubin exceeds 2 times ULN.
- Creatinine value exceeds 1.5 times ULN.
- [redacted]
- Positive urine drug screen or alcohol breath test.
- Requires a medication that is prohibited by the protocol (refer to Section 8.9.1).

All subjects prematurely discontinuing the study, regardless of cause, should have all early termination assessments performed (see Section 8.7.4.2).

8.10.2. Handling of Withdrawals

If a subject prematurely withdraws from the study, either at his/her request or at the investigator's discretion, the investigator will record the reason for withdrawal on the relevant eCRF. All subjects who withdraw from the study prematurely will be asked to have all early termination assessments performed within 4 weeks.

It is crucial to obtain follow-up data for any subject withdrawn because of an AE, abnormal laboratory test, vital sign measurement, physical examination, or ECG finding. In any case, every effort must be made to undertake safety follow-up procedures.

8.10.3. Sponsor's Termination of Study

NBI reserves the right to discontinue the study at any time for clinical or administrative reasons. Such a termination must be implemented by the investigator if instructed to do so by NBI in a time frame that is compatible with the subjects' well-being.

9. STUDY DRUG

NBI-74788 will be supplied as capsules containing 50 mg of NBI-74788 [redacted] for oral administration.

9.1. Study Drug Supplies

NBI or its designee will provide the study center with sufficient capsule supplies for the completion of the study. Study drug will be supplied in [redacted].

9.2. Study Drug Packaging and Labeling

All packaging and labeling operations will be conducted according to Good Manufacturing Practice (GMP) and GCP. The study drug will be sent to designated staff at the study center who

must complete and return the Drug Supply Confirmation to NBI or its designee verifying the receipt of the drug.

Study drug will be labeled with the following information, including, but not limited to: protocol number, dosage form, route of administration, Sponsor name, and the statement "Caution – New Drug: Limited by Federal law to investigational use."

9.3. Study Drug Administration

Subjects will take a study drug capsule by mouth starting at approximately 1900 hours beginning on Day 1, and then at approximately 0700 hours and 1900 hours for 14 consecutive days. Study drug will be administered at the study center on Days 2 and 14 with subjects' breakfast and evening meals, respectively, and on Day 1 with subjects' evening meal. The subjects' usual morning dose of concurrent steroidal treatments, study drug dosing, and breakfast (snacks will be allowed prior to breakfast) will be delayed until after the 15 hour postdose PD samples are collected (ie, at approximately 1000 hours) on Day 2.

Each dose of study drug is to be administered a meal (breakfast or the evening meal); each meal should be completed within [redacted]. The date and time of study drug administration, the number of capsules taken, and confirmation that study drug was taken with breakfast and the evening meal will be documented each day.

9.4. Study Drug Storage and Return

NBI-74788 [redacted] and in a locked area accessible only to the pharmacist or designee until dispensing.

Study drug should be stored and inventoried according to applicable state and federal regulations and study procedures.

Written documentation to account for study drug and study drug materials is mandatory; all unused study drug and study drug materials must be kept in a secure location for final accountability and reconciliation. Returned study drug and study drug materials must be accounted for on a study drug return form provided by NBI or the designee. The investigator must provide a written explanation for any destroyed or missing study drug or study drug materials.

Returns will be shipped to NBI or its designee at the completion of the study according to instructions provided by NBI or its designee. Study drug return forms must be completed for the shipment of returns and sent with the study drug and study drug materials. One copy of the study drug return form will be retained in the investigator's study file. All returned study drug and study drug materials should be stored, inventoried, reconciled, and returned according to applicable state and federal regulations and study procedures.

9.5. Blinding

This is an open-label study.

9.6. Study Compliance and Accountability

All doses of the study drug ingested in the study center will be taken in the presence of study center personnel who will check the subject's hands and mouth to confirm that the dose has been swallowed.

The quantity of study drug dispensed, used, and returned will be recorded on a dispensing log or otherwise documented. The quantity of study drug lost or destroyed, must also be accounted for and documented. The designated pharmacist or qualified personnel will be responsible for maintaining accurate records of the quantity and dates of all study drug supplies received, dispensed, and returned.

The exact time of medication dosing will be recorded on the eCRF and in the subject diary.

10. ADVERSE EVENTS

All AEs, whether observed by the investigator, reported by the subject, noted from laboratory findings, or by other means, will be recorded from the time the subject has signed the ICF until the subject's final study visit.

10.1. Definition

An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AEs include, but are not limited to: (1) a worsening or change in nature, severity, or frequency of conditions present at the start of the study; (2) subject deterioration due to primary illness; (3) intercurrent illness; and (4) drug interaction.

All suicidal behaviors and clinically significant suicidal ideations will be documented as an AE.

Subjects should be questioned in a general way, without asking about the occurrence of any specific symptom. The investigator should attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE and not the individual signs/symptoms. Following questioning and evaluation, all AEs, whether believed by the investigator to be related or unrelated to the study drug, must be documented in the subject's medical records, in accordance with the investigator's normal clinical practice and on the AE eCRF. Each AE is to be evaluated for duration, intensity, frequency, seriousness, outcome, other actions taken, and relationship to the study drug.

The following are not considered AEs:

- Continuous persistent disease/symptom present before drug administration, unless it unexpectedly progresses, or increases in severity following drug administration.
- Pregnancy.

10.2. Intensity of Adverse Events

AEs must be graded for intensity. An intensity category of mild, moderate, or severe, as defined in Table 4, must be entered on the AE eCRF. It should be noted that the term "severe" used to grade intensity is not synonymous with the term "serious."

Table 4: Intensity of Adverse Events

Grade	Intensity
Mild	An AE 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 AE 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 AE that interrupts usual activities of daily living, or significantly affects clinical status, or may require intensive therapeutic intervention.

10.3. Relationship to Study Drug

The investigator will document his/her opinion of the relationship of the AE to treatment with study drug using the criteria outlined in Table 5. An AE is deemed associated with the use of the study drug "if there is a reasonable possibility that the drug caused the AE" (otherwise referred to as a suspected adverse reaction). Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE (Title 21 CFR 312.32 [a]).

Table 5: Relationship of Adverse Events to Study Drug

Relationship	Description
Definite	A reaction that follows a reasonable temporal sequence from administration of the drug or in which the drug level has been established in body fluids or tissue; that follows a known or expected response pattern to the suspected drug; and that is confirmed by improvement on stopping or reducing the dosage of the drug, and reappearance of the reaction on repeated exposure.
Possible	An AE in which there is reasonable possibility that the drug caused the event. Reasonable possibility means there is evidence to suggest a causal relationship between the drug and the AE.
Unlikely	A reaction that follows a reasonable temporal sequence from administration of the drug; that follows a known or suspected response pattern to the suspected drug; but that could reasonably be explained by known characteristics of the subject's clinical state.
Not Related	Any event that does not meet the above criteria.

10.4. Recording Adverse Events

For enrolled subjects, each AE will be listed as a separate entry on an AE eCRF. Screen failure subjects will have AE information noted in the source documentation. The investigator (or designee) will provide information on dates and times of onset and resolution, intensity, seriousness, frequency, action(s) taken, changes in study drug usage, relationship to study drug, and outcome.

The following categories of medical events that could occur during participation in a clinical study must be reported within 24 hours to NBI or its designee:

- SAE, including death (Section 10.6).
- Pregnancy (Section 10.7).
- Events of suicidal behavior or suicidal ideation type 4 (active suicidal ideation with some intent to act, without specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the C-SSRS.

10.5. Post-Study Follow-Up of Adverse Events

All AEs, including clinically significant changes in ECGs, physical examination findings, or isolated clinically significant laboratory findings must be followed until the event resolves, the condition stabilizes, the event is otherwise explained, or the subject is lost to follow-up.

AEs ongoing at the final study visit (or upon early termination) will be followed for as long as necessary to adequately evaluate the subject's safety or until the event stabilizes or resolves or until the subject is lost to follow up. The investigator is responsible for ensuring that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals, as is practical.

10.6. Serious Adverse Events

All SAEs will be recorded from the time the subject has signed the ICF until the final study visit. Investigators are not obligated to actively seek SAEs after a subject has withdrawn from or completed the study. However, if the investigator learns of any SAE, including a death, at any time after a participant has been withdrawn from or has completed the study, and the investigator considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the Sponsor as described in Section 10.6.3.

10.6.1. Definition of a Serious Adverse Event

An SAE is any AE that results in any of the following outcomes:

- Death.
- A life-threatening AE. Life threatening means that the subject was, in the view of the investigator or Sponsor, at immediate risk of death from the reaction as it occurred. It does not mean that hypothetically the event might have caused death if it occurred in a more serious form.
- Inpatient hospitalization or prolongation of existing hospitalization. Hospitalization for elective treatment or a pre-existing condition that did not worsen during the clinical investigation is not considered an AE. Hospitalization or nursing home admission for the purpose of caregiver respite is not considered an AE. Complications that occur during hospitalization are AEs, and if a complication prolongs hospitalization, the event is considered serious. Treatment in a hospital emergency room is not a hospitalization.
- A persistent or significant incapacity or substantial disruption of a person's ability to conduct normal life functions.

- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life threatening, or require hospitalization. These events may be considered serious when, based on appropriate medical judgment, they may jeopardize the health of the subject and may require medical or surgical intervention to prevent one of the outcomes listed. Any other event thought by the investigator to be serious should also be reported, following the reporting requirements detailed in this section. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias, convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

10.6.2. Managing Serious Adverse Events

Subjects experiencing an SAE or an emergency situation will be examined by a physician as soon as possible. The physician in attendance will do whatever is medically needed for the safety and well-being of the subject. The subject will remain under observation as long as medically indicated. Appropriate laboratory studies will be conducted until all parameters return to normal or are otherwise explained or stable. The subject will be followed until the SAE resolves or until the subject is medically stabilized. The investigator (or designee) will notify the NBI Medical Monitor (and the IRB, if necessary) immediately (within 24 hours) of the SAE and the outcome of the SAE.

10.6.3. Reporting Serious Adverse Events and Other Immediately Reportable Events

Serious AEs and other immediately reportable events (defined in Section 10.4) must be reported within 24 hours of first knowledge of the event by study personnel to the NBI Medical Monitor or NBI Drug Safety and Pharmacovigilance (DSPV) Department. Reports of SAEs or pregnancies should be followed by a fax or email of the SAE or Pregnancy Form. It is important that the investigator provide his or her assessment of relationship to study drug at the time of the initial SAE report.

For SAEs or Other Immediately Reportable Events, contact DSPV:

DSPV telephone: [redacted]
DSPV facsimile: [redacted]
DSPV e-mail: [redacted]
NBI Medical Monitor: **Telephone:** [redacted]
Cell phone: [redacted]

10.6.4. Expedited Safety Reports

NBI or its representatives will submit an Expedited Safety Report for any suspected adverse reaction (as defined in Section 10.3) that is considered both serious and unexpected within 15 calendar days and for any unexpected fatal or life threatening experience within 7 calendar days via telephone or facsimile; or according to country specific regulations.

NBI or its representatives will send copies of each safety report submitted to regulatory authorities to the investigators. The safety report must be submitted to the appropriate IRB as soon as possible. Documentation of the submission to the IRB and receipt by the IRB (if applicable) must be retained for each safety report.

10.7. Pregnancy

Females of childbearing potential will be enrolled in this study. In the event of a pregnancy, the following instructions should be followed.

Pregnancy is neither an AE nor an SAE unless the criteria for an SAE are met. However, all pregnancies in female subjects who received NBI-74788 will be followed to assess for congenital anomaly. Subjects of childbearing potential must be counseled at all visits to continue using contraception (see inclusion criterion #8) until 30 days (females) or 90 days (males) after the last dose of study drug. If at any time between the time the subject signs the ICF and the last study visit a subject believes she is pregnant, the subject will be instructed to return to the study center within 24 hours and undergo a serum pregnancy test to confirm pregnancy.

All confirmed pregnancies in subjects who received study drug must be immediately reported to NBI (refer to Section 10.6.3 for contact information), followed by fax or email of the pregnancy form to NBI DSPV. A first trimester ultrasound will be requested for all confirmed pregnancies. Pregnancies in subjects who received NBI-74788 will be followed until resolution (ie, termination [voluntary or spontaneous] or birth).

11. DOCUMENTATION OF DATA

11.1. Case Report Forms

The case report form data for this study are being collected with an electronic data capture (EDC) system [redacted] The EDC system and the study-specific eCRFs will comply with Title 21 CFR Part 11. The documentation related to the validation of the EDC system is available through the vendor, [redacted] while the validation of the study specific eCRFs will be conducted by NBI and the required documentation will be maintained in the Trial Master File.

The investigator will document subject data in his/her own subject files. These subject files will serve as source data for the study. All eCRF data required by this protocol will be recorded by authorized study personnel in the EDC system, with the exception of data captured in an electronic format, which will be loaded electronically into the appropriate eCRFs. All data entered into the eCRF will be supported by source documentation. The eCRF for each subject must be reviewed by the investigator and signed on the appropriate eCRF page(s). This should be done as soon as possible after the subject completes the study.

The investigator or an authorized member of the investigator's staff will make any necessary additions/corrections to the eCRF. All change information, including the date, person performing the corrections, and reason for the change will be available via the electronic audit

trail, which is part of the EDC system. The eCRFs will be reviewed periodically for completeness, legibility, and acceptability by NBI (or designee). NBI will also be allowed access to all source documents and medical records pertinent to the study in order to verify eCRF entries. The Principal Investigator will review the eCRFs for completeness and accuracy and enter his or her electronic signature on the eCRFs as evidence thereof.

[redacted] will provide access to the NBI portal of the EDC system for the duration of the study through a password-protected method of internet access. Such access will be removed from investigator sites at the end of the site's participation in the study. Data from the EDC system will be archived on appropriate data media and provided to the investigator at that time as a durable record of the site's eCRF data. Although not required, the investigator may make paper printouts from that media.

All clinical work conducted under this protocol is subject to GCP regulations. This includes an inspection by NBI and/or health authority representatives at any time. The Principal Investigator will agree to the inspection of study-related records by health authority representatives and/or NBI.

11.2. Data Capture, Review, and Validation

Data entered in the EDC system will be verified against the source data by NBI (or designee). Any discrepancies will be corrected on-line by authorized site personnel. Automated (computer-generated) logic checks will run in order to identify items such as inconsistent study dates. In addition, manual review/checks may be conducted by NBI on the data. Any inconsistencies/errors/omissions identified will be sent to the site (via an electronic query) for the necessary corrections to be made to the eCRF. Once entered and saved in an eCRF, data immediately become part of the study database and are available to NBI.

11.3. Coding Dictionaries

AEs and medical history will be coded using the chosen version of the Medical Dictionary for Regulatory Activities (MedDRA). Prior and concomitant medications will be coded using the chosen version of the World Health Organization Drug Dictionary (WHODrug).

12. STATISTICAL AND ANALYTICAL PLAN

Descriptive statistical methods will be used to summarize the data from this study. The term “descriptive statistics” refers to the number of subjects (n), mean, median, SD, SEM, minimum, and maximum for continuous variables, and refers to the number of subjects (or events) and percentage for categorical variables. Confidence intervals may be presented for selected variables as well.

Detailed descriptions of the data summaries that will be presented for this study will be provided in the expanded Statistical Analysis Plan (SAP). The SAP will be developed prior to locking the study database.

12.1. Analysis Sets

Data summaries for this study will be based on the safety analysis set, which will include all subjects who receive a dose of study drug. Additional analysis sets may be specified in the SAP.

12.2. Sample Size

The sample size for this study is based on practical clinical considerations with no formal statistical power calculations.

12.3. Handling of Missing Data

All available study data will be included in relevant summaries and data displays, including any available data for subjects with incomplete or missing data.

12.4. Disposition of Subjects

A summary of subject disposition will be prepared that displays the number of subjects who were enrolled, received study drug, and completed the study. The number of subjects who did not complete the study will be displayed both overall and by reason for discontinuation.

12.5. Demographics and Baseline Characteristics

Age, height, weight, BMI, gender, race, ethnic group, [redacted], and screening 17-OHP levels will be summarized with descriptive statistics.

12.6. Pharmacokinetic Data

Descriptive statistics and graphical displays will be presented for NBI-74788 and metabolites plasma concentrations by scheduled sampling time. For these summaries, values that are below the limit of quantitation (BLQ) will be set equal to zero.

Individual subject plasma concentration vs. time plots will also be presented.

The following plasma PK parameters will be calculated for NBI-74788 and metabolites using noncompartmental methods and summarized by dose cohort using descriptive statistics:

- Area under the plasma concentration versus time curve from 0 to 12 hours ($AUC_{0–12}$)
- C_{max}
- Time to reach C_{max} (t_{max}).

Additional PK parameters for Day 14 to 15 only:

- Average plasma concentration at steady state (C_{avg})
- Percent fluctuation at steady state (%fluctuation)
- Accumulation ratio at steady state
- $t_{½}$
- Apparent terminal rate constant (λz)
- Apparent mean residence time (MRT)

- Apparent systemic clearance after oral administration (CL/F) (NBI-74788 only).

12.7. Pharmacodynamic Data

[redacted] Morning 17-OHP (serum; ng/dL) from the 8- and 12-hour postdose samples (collected at 0300 and 0700 hours).

[redacted] 17-OHP at all other times, androstenedione (serum; ng/dL), testosterone (serum; ng/dL), cortisol (serum; µg/dL), and adrenocorticotropic hormone (ACTH; plasma; pg/mL). Summaries of PD measures will include both observed values and changes from timepoint-matched PD baseline values.

12.8. Safety Data

TEAEs, categorized by system organ class (SOC) and/or preferred term as defined by MedDRA, will be summarized. A TEAE is defined as any AE that occurs after the first dose of study drug. Any AE that occurred before the first dose of study drug will be considered a pretreatment AE. The TEAE tables will include the number and percentage of unique subjects experiencing each event.

Clinical laboratory data, vital sign measurements, ECG data, and other safety data will be summarized by timepoint (as appropriate) with descriptive statistics.

12.9. Interim Analysis

An interim analysis is not planned for this study.

13. REGULATORY AND ETHICAL ISSUES

13.1. General Legal References

The study will be carried out according to the provision of the US CFR, the US Food and Drug Administration (FDA), Canada Food and Drugs Act and Regulations, Health Canada, and the ICH Guidelines for GCP. All clinical work conducted under this protocol is subject to GCP rules. This includes an inspection by NBI or its representative, health authority, or IRB representatives at any time. The investigator must agree to the inspection of study-related records by health authority representatives and/or NBI or its designee.

13.2. Institutional Review Board

The final approved protocol and the consent/assent documents will be reviewed by the IRB for the clinical site. The committee's decision concerning conduct of the study will be sent in writing to the investigator and a copy will be forwarded to NBI. The investigator must agree to make any required progress reports to the IRB, as well as reports of SAEs, life threatening problems, or death.

13.3. Protocol Adherence and Amendments

The protocol must be read thoroughly, and the instructions must be followed exactly. Any changes in the protocol will require a formal amendment. Such amendments will be agreed upon and approved in writing by the investigator and NBI. The IRB will be notified of all amendments to the protocol. Amendments to the protocol will not be implemented until written IRB approval has been received.

13.4. Required Documents

The investigator must provide NBI or its representatives with the following documents before the enrollment of any subject (originals should be kept by the investigator in the investigator's regulatory document binder):

- Signed copy of the approved protocol signature page.
- Investigator's Brochure acknowledgement page.
- Completed and signed statement of investigator (Form FDA 1572) and/or Clinical Trial Site Information Form, as applicable.
- Curriculum vitae and current medical license of the investigator and subinvestigators.
- Financial disclosure information as required.
- Letter of approval from the IRB for the protocol and consent documents.
- Copy of the IRB approved written ICF to be used.
- Laboratory documents (certifications/accreditations, normal ranges) if not provided by a central laboratory.

13.5. Informed Consent

Parent(s) or legal guardian(s) will provide informed consent with signed (or verbal, if applicable) and witnessed study subject assent before the performance of any study-related procedures.

Each subject's chart will include the signed ICF with signed and witnessed study subject assent (or confirmation of verbal assent) for study participation. When the study treatment is completed and the eCRF has been monitored, the ICF and signed and witnessed study subject assent will be kept in the investigator's central study file. Regulatory authorities may check the existence of the signed ICF and the signed and witnessed study subject assent in this central study folder.

13.6. Study Monitoring

Throughout the course of the study, the study monitor will make frequent contacts with the investigator. This will include emails, telephone calls, and on-site visits. During the on-site visits, the eCRFs will be reviewed for completeness and adherence to the protocol. As part of the data audit, source documents will be made available for review by the study monitor. The study monitor will also perform drug accountability checks and may periodically request review of the investigator study file to ensure completeness of documentation in all respects of clinical study conduct.

Upon completion of the study, the study monitor will arrange for a final review of the study files after which the files should be secured for the appropriate time period. The investigator or appointed delegate will receive the study monitor during these on-site visits, will cooperate in providing the documents for inspection, and respond to inquiries. In addition, the investigator will permit inspection of the study files by authorized representatives of the regulatory agencies.

13.7. Quality Assurance

The study will be conducted in accordance with NBI's standard operating procedures designed to ensure that all procedures are in compliance with GCP, FDA Guidelines, Health Canada Guidelines, and according to national law. Quality assurance audits may be conducted at the discretion of NBI.

13.8. Record Retention

Federal regulations require that records of drug disposition, eCRFs, and all reports of this investigation shall be retained by the investigator for a minimum of 2 years after notification by NBI that the regulatory authorities have been notified of the study's termination, or 2 years after approval of the marketing application. If the investigator is unable to retain the study documents for the required amount of time, NBI must be informed of the individual who will be assuming this responsibility.

13.9. Confidentiality

NBI and the clinical site affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, all data will be identified only by an identification number.

All information concerning this study and which was not previously published is considered confidential information. This confidential information shall remain the sole property of NBI; it shall not be disclosed to others without written consent of NBI; and shall not be used except in the performance of this study.

The information compiled during the conduct of this clinical study is also considered confidential and may be disclosed and/or used only by NBI as deemed necessary. To allow the use of the information derived from this clinical study and to ensure compliance with current federal regulations, the investigator is obliged to furnish NBI with the complete test results and all data compiled in this study.

14. STUDY COMMENCEMENT AND DISCONTINUATION

Upon satisfactory receipt of all required regulatory documents, NBI (or designee) will arrange that all study material be delivered to the study center. Subject entry should not begin until after the required regulatory documents are confirmed as received, and the Investigator Meeting/Initiation Meeting has occurred. All personnel expected to be involved in the conduct of the study will undergo orientation to include review of study protocol, instructions for eCRF

completion, AE reporting, and overall responsibilities including those for drug accountability and study file maintenance.

If the study is discontinued, all subjects should undergo a complete follow up examination. Any clinically relevant finding, including laboratory values of potential clinical concern, and adverse experiences will be followed until they resolve or return to a clinically acceptable level.

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