CLINICAL STUDY PROTOCOL

A Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Phase 2 Dose-Response Study to Determine Safety and Effectiveness of Two Concentrations of NFX-179 Gel in Subjects with Cutaneous Neurofibromas

Protocol No.	NFX-179-NF1-202
Protocol Date:	06-NOV-2023
Amendment No.	5
Supersedes:	04-AUG-2023
Sponsor:	NFlection Therapeutics 867 Boylston Street, 5th Floor #1116 Boston, MA 02116 United States
Medical Monitor:	[redacted] 24-hour telephone: [redacted] Medical Monitor Email: [redacted] SAE Email: [redacted]

PROTOCOL INVESTIGATOR SIGNATURE PAGE
Number: NFX-179-NF1-202

INVESTIGATOR COMMITMENT:

I will provide copies of the protocol, any subsequent protocol amendments and access to all information provided by NFlection to the investigational center staff under my supervision. I will discuss this material with them to ensure that they are fully informed about the Investigational Medicinal Product and the study protocol.

I agree to conduct this clinical study according to the attached protocol, except when mutually agreed to with NFlection in writing. I also agree to conduct this study in compliance with all local regulatory requirements, Good Clinical Practices, as well as with the requirements of the appropriate Institutional Review Board(s) /Ethics Committee(s) and any other Institutional requirements.

_____

Printed Name of Investigator

_____

Signature of Investigator

_____

Date

PROTOCOL APPROVAL PAGE

Protocol Number: NFX-179-NF1-202

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Protocol No.	NFX-179-NF1-202
Sponsor:	NFlection Therapeutics 867 Boylston Street, 5th Floor #1116 Boston, MA 02116 United States

[redacted]

Date

NFlection Therapeutics

SYNOPSIS

Name of Sponsor:	NFlection Therapeutics, Inc.
Name of Investigational Product:	NFX-179 Topical Gel
Name of Active Ingredient:	NFX-179
Title of Study:	A Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Phase 2 Dose-Response Study to Determine Safety and Effectiveness of Two Concentrations of NFX-179 Gel in Subjects with Cutaneous Neurofibromas
Phase of Development:	2
Investigational Centers:	Approximately 27 United States investigational centers
Study Period:	Approximately 238 days
Duration of Treatment:	182 days of once-daily (QD) application to 10 Target cutaneous neurofibromas (cNF)
Duration of Subject Participation:	Approximately 242 days: • Screening period: Up to 28 days • Treatment period: 182 days • No treatment follow-up period: 28 days (plus an allowable 4-day window).
Objectives:	Primary Objectives: • To determine the effectiveness of each of two concentrations of NFX-179 Gel [redacted] compared with Vehicle Gel applied QD for 182 days • To determine the safety of NFX-179 for each active treatment group compared with the vehicle group after 182 days of QD treatment. Efficacy Objectives: • To determine the effect of NFX-179 Gel defined as the percent of responders after 182 days of treatment • To determine the effect of NFX-179 Gel defined as the percent change in cNF volume after 182 days of treatment based on cNF volume derived from ruler measurements • To determine the effect of treatment with NFX-179 Gel as the change from baseline in the Physician's Tumor Assessment after 182 days of treatment • To determine the effect of treatment with NFX-179 Gel as the change from baseline in the Subject's Self-Assessment after 182 days of treatment Exploratory Efficacy Objective: • To determine the effect of treatment with NFX-179 Gel as the change from baseline in the individual Patient Reported Outcome Measurements after 182 days of treatment.

Endpoints:	Safety Endpoints:
	• Safety of NFX-179 for each treatment group compared with the vehicle group after 182 days of QD treatment.
	Efficacy Endpoints:
	• Primary Efficacy Endpoint:
	  • Percent of responders, defined as at least 50% reduction in cNF volume above the surrounding non-tumor skin determined from ruler measurements after 182 days of QD applications of NFX-179 Gel
	• Secondary Efficacy Endpoints:
	  • Percent change in cNF volume after 182 days of QD applications of NFX-179 Gel based on cNF volume derived from ruler measurements
	  • Effect of treatment with NFX-179 Gel as the change from baseline in the Physician's Tumor Assessment
	  • Effect of treatment with NFX-179 Gel as the change from baseline in the Subject's Self-Assessment
	• Exploratory Efficacy Endpoint:
	  • Effect of treatment with NFX-179 Gel as the change from baseline in each of the Patient Reported Outcome Measurements after 182 days of treatment

Number of Subjects:	Approximately 168 subjects (≥ 18 years of age) with a clinical diagnosis of NF1 that meet the enrollment criteria will be randomized in the study. With a 1:1:1 randomization ratio, it is anticipated that at least the following number of subjects will complete the study: • 50 subjects randomized to receive NFX-179 Gel [redacted] • 50 subjects randomized to receive NFX-179 Gel [redacted] • 50 subjects randomized to receive Vehicle Gel
Study Design:	This is a randomized, double-blind, vehicle-controlled, parallel group dose-response study evaluating the safety and effectiveness of 2 concentrations of NFX-179 Gel in subjects with cutaneous neurofibromas. At Visit 1, the investigator will identify 10 Target cNFs that fulfill the enrollment criteria. The Target cNFs must be located on the subject's face, anterior trunk, or upper extremities. Preferably 2 Target cNFs are located on the face and 8 Target cNFs are located on the anterior trunk or upper extremities. Alternatively, at least 1 Target cNF is located on the face, in which case 9 Target cNFs must be located on the anterior trunk or upper extremities. The study medication will be applied topically QD to the Target cNFs for 182 days (26 weeks). During the duration of the study subjects will be evaluated for safety and efficacy. A Coordinating Investigator, [redacted], is designated by the Sponsor.

	The Coordinating Investigator is responsible for the overall conduct of the study and signing the Clinical Study Report on behalf of the participating site investigators upon study conclusion.

Main Criteria for Inclusion:	Select Inclusion Criteria:
	• Subject is at least 18 years of age
	• Subject must provide written informed consent prior to any study procedures
	• Subject has 10 clinically diagnosed Target cNFs with preferably 2 Target cNFs located on the face and 8 Target cNFs located on the anterior trunk or upper extremities. Alternatively, at least 1 Target cNF is located on the face, in which case 9 Target cNFs must be located on the anterior trunk or upper extremities. Each Target cNF must meet the following criteria:
	  • Has, in the investigator's opinion, a clinically typical appearance
	  • Is not within 1 centimeter of the orbital rim
	  • Is not covered with hair that might, in the investigator's opinion, interfere with obtaining photographs or impair evaluation of the cNF
	  • Has a Physician's Tumor Assessment grade ≥2
	  • Is dome shaped
	  • Is not pedunculated
	  • Is a discrete cNF surrounded by sufficient non-affected skin that, in the investigator's opinion:
	  • The dimensions can be measured
	  • The perimeter can be outlined in the study photographs
	  • Is not irritated (*e.g.*, bleeding, inflamed)
	  • Is not in an area subject to repeated trauma (*e.g.*, area that is shaved, on the beltline, under a bra strap, etc.)
	  • Does not have an active cutaneous infection
	  • Target cNFs on the face must have the following tumor dimensions:
	  • a length that is ≥5mm and ≤14mm
	  • a width that is ≥5mm and ≤14mm
	  • a height that is ≥2mm.
	  • Target cNFs on the anterior trunk or upper extremities must have the following tumor dimensions:
	  • a length that is ≥7mm and ≤14mm
	  • a width that is ≥5mm and ≤14mm
	  • a height that is ≥2mm
	• Female subjects who are women of childbearing potential must have a negative urine pregnancy test result and be willing to use a protocol approved contraceptive method for the duration of the study.
	
	Select Exclusion Criteria:
	• Subject has used any of the following topical therapies within the

	specified period prior to Visit 2 on or in proximity to any Target cNF that, in the investigator's opinion, impairs evaluation of a Target cNF or which exposes the subject to an unacceptable risk by study participation: • Corticosteroids; 30 days • Prescription retinoids (*e.g.*, tazarotene, tretinoin, adapalene); 30 days • > 5% of an alpha-hydroxy acid (*e.g.*, glycolic acid, lactic acid); 30 days • Fluorouracil; 30 days • Imiquimod; 30 days • LASER light (*e.g.*, intense pulsed light [IPL], photo-dynamic therapy [PDT] or other energy-based therapy; 180 days • Any Target cNF has ever been treated with a topical MEK inhibitor or a topical BRAF inhibitor • The Subject has used any of the following systemic therapies within the specific period prior to Visit 2: • Retinoids (*e.g.*, etretinate, isotretinoin); 90 days • MEK inhibitors; 180 days • BRAF inhibitors; 180 days • Subject has a history of hypersensitivity to any of the ingredients in the study medications • Subject has any known intercurrent illness or physical condition that would, in the investigator's opinion, impair evaluation of a Target cNF or which exposes the subject to an unacceptable risk by study participation • Subject has any condition (*e.g.*, other skin conditions or diseases, metabolic dysfunction, physical examination findings, clinical laboratory findings) or situation (*e.g.*, vacation, scheduled surgery) that would, in the investigator's opinion, impair evaluation of a Target cNF or which exposes the subject to an unacceptable risk by study participation Subject has participated in an investigational drug trial in which administration of an investigational study medication occurred within the previous 30 days.
Study Medication, Dosage and Mode of Administration	NFX-179 Gel or Vehicle Gel for topical application QD for 182 days to 10 Target cNFs: • NFX-179 Gel [redacted] for topical administration, QD for 182 days • NFX-179 Gel [redacted] for topical administration, QD for 182 days • Vehicle Gel for topical administration, QD for 182 days
Criteria for Evaluation	***Safety Assessments***: Adverse Events: During the study, subjects will be assessed for the occurrence of new and ongoing AEs. Descriptions of AEs will include the date(s) of onset and resolution (if resolved), maximum severity, and seriousness, action taken regarding the study drug, corrective treatment, outcome, and the investigator's assessment of causality. AEs present at any visit will be followed to resolution

	(return to normal or to the baseline state) or until clinically stable as determined by the investigator. Clinical Laboratory Safety Tests: At Visits 1, 2, 4 and 8 routine safety laboratory tests (CBC/differential, serum chemistry, and urinalysis) will be performed. Local Tolerability: At Visits 2-9 local tolerability on each Target cNF will be evaluated through assessment of selected signs (*i.e.*, erythema, edema, scabbing/crusting, vesiculation and erosion) and symptoms (*i.e.*, stinging, burning and pruritus [itching]) of local tolerability. Medical History: At Visit 1 medical history information will be reported for each subject. At Visit 2 medical history will be updated as needed. Physical Examination: At Visit 1 a physical examination will be performed. Vital Signs: At Visits 1, 2, 8 and 9 vital signs will be measured. Pregnancy Tests: At Visits 1, 2, 4, 5, 6, 7, 8 and 9 female subjects who are women of childbearing potential will have a urine pregnancy test performed. ***Efficacy Assessments***: Target cNF dimensions: At Visits 1, 2, 4, 5, 6, 7, 8 and 9 the investigator will measure the length, width, and height of each Target cNF using a ruler. Physician's Tumor Assessment: At Visits 1, 2, 4, 5, 6, 7, 8 and 9 the investigator will perform a Physician's Tumor Assessment of the severity of each Target cNF. Subject's Self-Assessment: At Visits 2, 4, 5, 6, 7, 8 and 9 each subject will perform a Subject's Self-Assessment of the severity of each Target cNF ***Other Assessments***: Demographics: At Visit 1 demographic characteristics will be reported for each subject. Pharmacokinetics: At select sites, blood samples for assessment of NFX-179 levels will be collected at Visit 4. Patient Reported Outcome Measurements: At Visits 2, 6 and 8 each subject will perform a Patient Reported Outcome Measure assessment of each Target cNF.

	Standardized Photography: At Visits 1, 2, 6, 8 and 9 standardized photographs will be taken of each Target cNF.
Statistical Methods	***Analysis Populations and Missing-Data Imputation:*** All subjects who were randomized and dispensed study drug and have at least one post-baseline visit with efficacy evaluations will be included in the intent-to-treat (ITT) population. The Observed Cases (OC) population will include all subjects in the ITT population with observed efficacy data at Visit 8. No data imputation will be used in this population for subjects with missing data at any post-baseline visit. The Observed Cases (OC) population will be used for primary and secondary efficacy analyses to address the main efficacy evaluation objective of the study. There will also be two sensitivity analyses of efficacy. For the first sensitivity analyses, the Per-Protocol (PP) population, drawn from the OC population subjects who completed the study through Visit 8 with no major protocol violations, will be used. For the second sensitivity analyses, the ITT population will be used, and all missing post-baseline efficacy data will be imputed using last observation carried forward (LOCF) from the last available observed efficacy data after the Baseline visit. Mixed Model-based missing data imputation or Multiple Imputation may be used as a supplementary imputation method. A supplemental efficacy analysis based on subject Responders will also be conducted using the ITT population where subjects terminating the study before completing Visit 8 due to treatment-related adverse events will be imputed as Non-Responders. All subjects who are randomized, received at least one confirmed dose of study drug, and have at least one post-baseline safety evaluation will be included in the Safety Population. All efficacy analyses will perform separate comparisons of each Active treatment group with the Vehicle group along with other contrasts described below. No adjustments for multiplicity will be made. ***Safety****:* Safety Endpoints: • Adverse events • Local tolerability including: o erythema o edema o scabbing/crusting o vesiculation o erosion o stinging o burning o pruritis • Clinical laboratory assessments. ***Statistical Analyses:*** Overview:

	Analyses of efficacy parameters collected at the tumor level will primarily be performed at the tumor level, under the assumption that tumor responses within the same subject will be predominantly statistically independent. Those parameters include results based on tumor dimensions, SSA and PTA evaluations, and responder analyses based on any of these measures. This approach is consistent with the topical application of the study medication to individual tumors and the assumption of minimal systemic absorption or systemic action of the study medication. The statistical assumption of within-subject tumor response independence will be evaluated using the appropriate Shrout-Fleiss intraclass correlation based on tumor changes from baseline. For this study, that statistic is assumed to be less than [redacted] Analyses conducted at the subject level will then be performed as supplementary analyses. Tumor dimension analyses will include tumor volume derived from measurements by ruler, which will be the primary assessment. Tumor volume is the primary measurement of interest; however, the ruler measurements of tumor length, width, height and area will also be analyzed as supplementary analyses, using the analysis models applied to tumor volume. If the Shrout-Fleiss intraclass correlation statistic is equal to or greater than [redacted] then subject-level efficacy parameter analyses will be considered primary, and tumor-level efficacy parameter analyses will be considered supplementary. In either case, results from both types of analyses will be presented. <u>Contrasts:</u> In order to fully understand the dose response results and achieve greater sensitivity to detect effectiveness for the active treatments, comparisons among the three treatment groups will include the following: pairwise contrasts between each active treatment group vs vehicle; a contrast between the [redacted] treatment group and the [redacted] treatment group; and a contrast between the average of the [redacted] and [redacted] treatment groups vs vehicle. In addition, all analyses and contrasts will be conducted separately for each lesion body location: Face, anterior trunk, and upper extremities. <u>Endpoints:</u> The safety endpoint is to determine the safety of treatment with NFX-179 Gel [redacted] and [redacted] or Vehicle Gel applied QD for 182 days of treatment. The results of safety and local tolerability assessments including pain/burning, itching, erythema, edema, scabbing/crusting, and vesiculation/erosion will be summarized by treatment group and visit. The evaluation of adverse events will be based on summaries and listings of adverse events by treatment group, as described below under Safety Analyses. If tumor independence is confirmed as discussed above, the primary efficacy endpoint will be a dichotomized analysis conducted on the proportion of tumors achieving a reduction from baseline volume of at least 50%. A Chi-square analysis at the tumor level will be performed as the primary analysis between vehicle and each active treatment group. Otherwise if tumor

	independence is not confirmed, the primary efficacy endpoint will be analyzed at the subject level. The primary efficacy analysis will then be a dichotomized Chi-square Responder analysis at the subject level. It will be based on the proportion of subjects considered to be Responders, where a Responder is defined as a subject for whom at least 5 treated tumors showing the greatest tumor-level percent reduction from baseline volume have a percent reduction from baseline volume of at least 50%. A Chi-square analysis with contrasts as outlined above will be used. At the subject level analysis, an Analysis of Variance will also be used to analyze the per-subject mean percent of tumor responders, with contrasts as described above. Treatment groups may also be compared using appropriate mixed-model logistic regression incorporating both tumor- and subject-level information. Supplementary analyses similar to those described above will also be conducted based on threshold reductions from baseline volume of at least 25%, 30%, 60% and 75%. The first secondary efficacy endpoint will analyze the clinical efficacy of NFX-179 Gel defined as the mean percent change in neurofibroma volume after 182 days of treatment based on tumor volume derived from ruler measurements. Analyses of Variance will be conducted both on the tumor level and the subject level, including the contrasts as described above. The determination of whether the tumor-level or subject-level analysis will be considered primary will be based on the outcome of the tumor independence assessment as described above. The non-primary analysis will be considered as a supplementary analysis. Additional secondary efficacy endpoints include the analysis of change from baseline in the Physician's Tumor Assessment grades and the Subject's Self-Assessment grades after 182 days of treatment. These will be analyzed analogously to the primary endpoint using an Analysis of Variance and contrasts describe above. In addition, for each assessment dichotomized analyses will be conducted on the proportion of tumors achieving a grade of Clear, the proportion of tumors achieving a grade of either Clear or Almost Clear, and also the proportion of tumors achieving at least a 1 grade, and also a 2 grade or greater improvement from baseline after 182 days of treatment. Treatment groups will be compared using separate Chi-square analyses. An appropriate mixed-model logistic regression may also be used, as well as an ANOVA of within-subject averaged results across tumors. Contrasts as described above will be used. Analyses similar to those described above will be conducted based on changes and percent changes in tumor area, height, width and length. Efficacy analyses at post-baseline visits prior to Day 182 where efficacy data are collected will also be performed using the models described above. These will be considered exploratory in nature. ***Safety Analyses:***

	Subjects will be assessed for the occurrence of new and ongoing AEs. Descriptions of AEs will include the dates of onset and resolution (if resolved), maximum severity, seriousness, and action taken regarding the study drug, corrective treatment, outcome, and investigator's assessment of causality. All AEs will be recorded and classified using terminology from the Medical Dictionary for Regulatory Activities (MedDRA). All reported treatment-emergent AEs (TEAEs), defined as any AE with an onset on or after the date of first study drug application, will be summarized by treatment group, the number of subjects reporting TEAEs, system organ class, preferred term, severity, and relationship to study drug. When summarizing TEAEs by severity or relationship to study drug, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category. All reported serious adverse events (SAEs) will be summarized by treatment group, the number of subjects reporting SAEs, system organ class, preferred term, severity, and relationship to study drug. All information pertaining to AEs noted during the study will be listed by subject and will include a verbatim description of the event as reported by the investigator, as well as the preferred term, system organ class, start date, stop date (if stopped), seriousness, severity, action taken regarding the study drug, corrective treatment, outcome, and relationship to the study drug. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided as well as a listing of subjects who reported an SAE. Changes from baseline in local tolerability assessments and vital sign measurements will be summarized with descriptive statistics for each treatment group at all applicable study visits. Bioanalytical results from analysis of PK samples will be captured in a bioanalytical report, and summarized with descriptive statistics for each treatment group. Shift tables will be presented for changes in safety laboratory values to summarize laboratory test results collected at Screening, Baseline and End of Treatment visits. Normal ranges established by the central laboratory will be used to determine the shifts. A listing of all out-of-range laboratory test results at any assessment time point will also be provided. Determination of clinical significance for all out-of-range laboratory values will be made by each investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

1 CONTENTS

LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Definition
AE	Adverse Event
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	area under the curve
BSA	body surface area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
C_{max}	maximum observed plasma concentration
cNF	Cutaneous neurofibroma
CR	Clinically Relevant
CRF	Case Report Form
EC	Ethics Committee
ECG	electrocardiogram
eCRF	Electronic case report form
FIH	first-in-human
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
hERG	stably transfected human embryonic kidney
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICH	International Council for Harmonization
IRB	Institutional Review Board
LDH	Lactic Dehydrogenase
LTA	Local Tolerability Assessment
MEK	mitogen-activated protein kinase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
NCR	Not Clinically Relevant
NF1	Neurofibromatosis type 1
Nflection	Nflection Therapeutics
NOAEL	no-observed-adverse-effect level
PRN	As needed
PROM	Patient Reported Outcome Measure

PTA	Physician's Tumor Assessment
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SI	Subject Identifier
SOC	System Organ Class
SOP	Standard Operating Procedure
SSA	Subject's Self-Assessment
TEAE	Treatment Emergent Adverse Event
US	United States
WHO	World Health Organization

2 INTRODUCTION

Neurofibromatosis type I (*NF1*) is an autosomal dominant development syndrome caused by germline mutations in the *NF1* gene on chromosome 17. The *NF1* gene is responsible for production of a protein called neurofibromin that is involved in the RAS pathway and which is needed for normal function in many human cell types. *NF1* is one of the most common genetic disorders, is not limited by a person's race or sex, and causes tumors along the nervous system which can grow anywhere on the body.

A pathogenic variant in one allele of the *NF1* gene is sufficient for the development of *NF1*, although presentation varies widely. It is an age specific disease; most signs of *NF1* occur as the person ages and has hormonal changes. As of 2015, there were at least 100,000 people in the U.S. who have been diagnosed with NF1. A common symptom of *NF1* are benign skin tumors called cutaneous neurofibromas (cNFs) a common manifestation of *NF1*. The gene product neurofibromin negatively regulates RAS activity and acts as a tumor suppressor by preventing the activation of downstream signaling pathways such as the RAF/MEK/ERK pathway.

The severity of *NF1* varies widely, and little is known about what causes a person to have more severe or less severe cases. Sixty percent of people with *NF1* have mild cases, with few signs and symptoms and very little effect in their day-to-day lives. Forty percent of *NF1* patients however experience moderate to severe disease, which manifest as many, sometimes hundreds of cNFs that can grow anywhere on the body. These cNFs can have a dramatic and unpredictable effect on health-related quality of life and while they are rarely life-threatening, they can be the cause of social stigma and tremendous emotional and physical pain.

2.1 Study Rationale

NFlection tested the efficacy of a topical formulation of a novel MEK inhibitor (NFX-179) in an *ex vivo* model by using human cutaneous neurofibroma explants. Dose dependent suppression of the shared biomarker, p-ERK, by NFX-179 [redacted] was observed in human cutaneous neurofibroma explants. P-ERK suppression was not observed in neurofibroma explants treated with the vehicle formulation.

Western Blot analysis of p-ERK level showed complete suppression of p-ERK by all three dosages of NFX-179 in the top sections of the explant and a dose dependent suppression in the bottom sections.

Taken together, these data clearly demonstrate that NFX-179 [redacted] can penetrate human epidermis and suppress p-ERK in human cutaneous neurofibroma explants.

The NFX-179-NF1-201 study of NFX-179 Topical Gel applied once daily for 28 days in subjects with cNF tumors demonstrated the safety and tolerability of concentrations up to [redacted] and the potential therapeutic benefit of NFX-179 Gel to treat NF1 by reducing cNF tumor volume based on early clinical and biomarker evidence.

This study is designed to evaluate the dose response and efficacy of 2 concentrations of NFX-179 Gel [redacted] after 182 days (26 weeks) of once-daily (QD) application in subjects with *NF1* tumors.

2.2 Background

2.2.1 Nonclinical Experience

NFX-179 was evaluated for effects on cardiovascular, respiratory, and central and peripheral nervous systems in safety pharmacology studies. NFX-179 was found to block the hERG channel current with an IC_{50} value of [redacted] µM, which did not translate to any effect on the electrocardiogram (ECG) in the conscious dog. Doses achieving plasma levels of up to [redacted] ng/mL ([redacted] µM) at 2 hours post dose were without effect on ECG intervals, heart rate, and blood pressure or on tidal volume and respiratory rate and minute volume. Effects of oral NFX-179 on neurological function were assessed in male and female rats dosed with up to [redacted] mg/kg on Day 1 of the 28-day rat oral toxicity study; there were no effects on central and peripheral nervous system function with an NFX-179 C_{max} of [redacted] ng/mL in males and females, respectively.

In the minipig, topical administration of [redacted] w/w NFX-179 Gel results in very low systemic

exposure to NFX-179 with mean C_{max} and AUC_{last} values (male and female combined) of [redacted] ng/mL and [redacted] ng.h/mL, respectively, while high levels of NFX-179 were attained in the dermis/epidermis layers of the skin (up to [redacted] ng/g).

In the Good Laboratory Practice (GLP) 28-day dermal toxicology/toxicokinetic (TK) study, NFX-179 Gel was applied to minipigs topically with an application density of ([redacted] µL/cm^2 vs. [redacted] µL/cm^2) at up to [redacted] w/w. When measured 24 hours post dose after 28 days of administration, this dosing schedule resulted in high levels of NFX-179 in the dermis/epidermis layer of the skin related to the volume and concentration of the formulation applied while attaining relatively low levels of systemic exposure.

NFX-179 Gel was well-tolerated when applied dermally. There was sporadic and transient erythema, which was mostly graded as very slight (barely perceptible), with some episodes of well-defined erythema, and occasional but infrequent moderate erythema with occasional edema. There were no systemic effects at any dose level, including the highest dose level of [redacted] w/w NFX 179, equivalent to [redacted] mg/kg/day. The no observed-adverse-effect level (NOAEL) for this study was the lowest dose of [redacted] w/w applied to 10% body surface area (BSA) at [redacted] µL/cm2, equivalent to [redacted] mg/kg/day.

In the GLP 13-week dermal toxicology/TK study in minipigs, multiple animals, particularly in Groups 4 (initially [redacted] mg/kg/day, [redacted] and 5 (initially [redacted] mg/kg/day, [redacted] were placed on dose holiday for irritation at the dose site. The dose volume was reduced twice, on Day 19 (males)/Day 14 (females) to [redacted] and [redacted] mg/kg/day, respectively, and Day 68 (males)/Day 63 (females) to [redacted] mg/kg/day, respectively. Following 91 days of dermal administration of NFX-179 Gel, there were no adverse systemic effects; however, animals at [redacted] mg/kg/day ([redacted] Group 4) and [redacted] mg/kg/day ([redacted] Group 5) did not receive sufficient doses to evaluate the systemic toxicity following 91 days. These dose levels/dose concentrations were considered not tolerated due to multiple dose holidays and the need for pain management. The NOAEL for both local and systemic toxicity was [redacted] mg/kg/day ([redacted] Group 3). At the NOAEL in males and females, respectively, mean C_{max} was [redacted] and [redacted] ng/mL and mean $AUC_{0\text{-}24h}$ was [redacted] and [redacted] ng.hr.ng/mL.

Potential toxicities associated with increased systemic exposure were investigated in a GLP 28 day oral rat study where the NOAEL was [redacted] mg/kg/day with systemic exposures (C_{max} and

$AUC_{0\text{-}24h}$) of [redacted] and [redacted]-fold higher, respectively, for NFX-179 compared to plasma levels in the minipig following topical administration of a similar human equivalent dose. NFX-179 oral suspension was well tolerated in the rat at [redacted] mg/kg/day given orally with the spleen, liver, mesenteric lymph nodes, stomach, femur, ovaries, and skin/subcutis being the primary target organs for toxicity; the toxicities recorded at the NOAEL dose were either fully or partially reversible following a 14 day treatment-free period and were therefore considered non-adverse.

In the GLP 13-week oral toxicology/TK study in the rat, NFX-179 was well tolerated at dose levels of up to [redacted] mg/kg/day for 13 weeks, with toxicity limited to reductions in white blood cell counts in males at [redacted] mg/kg/day and red cell counts in females given [redacted] mg/kg/day, which were reversible following a 4-week treatment-free period. These findings correlated with increased incidence of adipocytes in the bone marrow and extramedullary haematopoiesis in the spleen at the end of the dosing period; however, as the peripheral blood changes were reversible, these microscopic findings were considered not to be adverse. The NOAEL was considered to be [redacted] mg/kg/day, equivalent to a C_{max} after 13 weeks of [redacted] or [redacted] ng/mL, and an $AUC_{0\text{-}24}$ of [redacted] or [redacted] ng.h/mL, in males and females, respectively.

NFX-179 was not mutagenic, clastogenic or aneugenic when evaluated in both in vitro and in vivo genetic toxicity tests. NFX-179 Gel was found to have no potential for skin sensitization, and there was no potential for eye irritation. NFX-179 showed high levels of light absorbance in the UV/Vis range, indicating that it has the potential to be phototoxic and photosensitizing.

Full details of the nonclinical studies for NFX-179 Gel are presented in the Investigator's Brochure.

2.2.2 Clinical Experience

NFlection Therapeutics, Inc. has completed the first-in-human (FIH) Phase 2a study. The NFX-179-NF1-201study was a 28-day double-blind, randomized, vehicle-controlled, parallel-group Phase 2a study to determine the safety, tolerability, pharmacokinetics, and pharmacodynamics of NFX-179 Gel [redacted] compared with vehicle in 48

subjects with cNF tumors. NFX-179 Gel applied once daily for 28 days at the 3 concentrations evaluated was shown to be safe and well tolerated. No treatment-related TEAEs and no acneiform rash were reported. There were few reports of signs and symptoms on the local tolerability assessments and almost all were mild and transient. There were no clinically relevant changes in laboratory parameters, vital signs, or ECGs. NFX-179 Gel demonstrated statistically significant dose-dependent suppression of p-ERK in cNF tumors in the [redacted] Gel groups [redacted] suppression, respectively) and a dose-related mean percent reduction in tumor volume at Day 28. Higher dose groups demonstrated a volume reduction that was correlated with p-ERK suppression.

Thus, in addition to demonstrating the safety and tolerability of concentrations up to [redacted] this study showed the potential therapeutic benefit of NFX 179 Topical Gel to treat NF1 by reducing cNF tumor volume based on early clinical and biomarker evidence.

Based on the results of the preclinical studies and NFX-179-NF1-201 Phase 2a study, the risk/benefit assessment supports evaluation of the [redacted] concentrations of NFX-179.

3 STUDY OBJECTIVES AND ENDPOINTS

The objectives of this study include the following:

Primary Objectives:

- To determine the effectiveness of each of two concentrations of NFX-179 Gel [redacted] compared with Vehicle Gel applied once daily (QD) for 182 days
- To determine the safety of NFX-179 for each active treatment group compared with the vehicle group after 182 days of QD treatment.

Efficacy Objectives:

- To determine the effect of NFX-179 Gel defined as the percent of responders after 182 days of treatment
- To determine the effect of NFX-179 Gel defined as the percent change in cNF volume after 182 days of treatment based on cNF volume derived from ruler measurements
- To determine the effect of treatment with NFX-179 Gel as the change from baseline in the Physician's Tumor Assessment after 182 days of treatment
- To determine the effect of treatment with NFX-179 Gel as the change from baseline in the Subject's Self-Assessment after 182 days of treatment.

Exploratory Efficacy Objective:

- To determine the effect of treatment with NFX-179 Gel as the change from baseline in the individual Patient Reported Outcome Measurements after 182 days of treatment

The endpoints being evaluated in this study include the following:
Safety endpoints:

- Safety of NFX-179 for each treatment group compared with the vehicle group after 182 days of QD treatment.

Efficacy endpoints:

- Primary Efficacy Endpoint:
  - Percent of responders, defined as at least a 50% reduction in cNF volume above the surrounding non-tumor skin determined from ruler measurements after 182 days of QD applications of NFX-179 Gel
- Secondary Efficacy Endpoints:
  - Percent change in cNF volume after 182 days of QD applications of NFX-179 Gel based on cNF volume derived from ruler measurements
  - Effect of treatment with NFX-179 Gel as the change from baseline in the Physician's Tumor Assessment
  - Effect of treatment with NFX-179 Gel as the change from baseline in the Subject's Self-Assessment
- Exploratory Efficacy Endpoint:
  - Effect of treatment with NFX-179 Gel as the change from baseline in each of the Patient Reported Outcome Measurements after 182 days of treatment

4 STUDY OVERVIEW

4.1 Study Design

This is a randomized, double-blind, vehicle-controlled, parallel group dose-response study evaluating the safety and effectiveness of 2 concentrations of NFX-179 Gel in subjects with cutaneous neurofibromas (cNF).

At Visit 1, the investigator will identify 10 Target cNFs that fulfill the enrollment criteria for treatment. The Target cNFs must be located on the subject's face, anterior trunk, or upper extremities. Preferably 2 Target cNFs are located on the face and 8 Target cNFs are located on the anterior trunk or upper extremities. Alternatively, at least 1 Target cNF is located on the face, in which case 9 Target cNFs must be located on the anterior trunk or upper extremities.

At Visit 2 (Day 1, Week 0) eligible subjects will be randomized and will begin the 182 day/26-week QD treatment period. The subject will apply the assigned study medication to the Target cNFs QD during the treatment period. The subject may have cNFs other than the Target cNFs but only the Target cNFs will be treated and evaluated.

Subjects will be seen at Visits 3-7 (Days 8, 29, 57, 85 and 141/Weeks 1, 4, 8, 12 and 20) for

follow-up visits during the treatment period.

At Visit 8 (Day 183/Week 26) subjects will be seen for the last treatment period visit and subjects will begin a 4-week no treatment follow-up period

At Visit 9 (Day 211/Week 30) subjects will be seen for an end of study visit.

No topical therapies for cNF other than the study medication may be used on any of the Target cNFs for the duration of the study.

As part of the clinical development program for NFX-179 Gel a subset of randomized subjects who complete this study (approximately 20%) may be invited to participate in an administratively separate exit interview study to learn about their experience in the study and to assist with their perception of clinically meaningful change in NF1.

A Coordinating Investigator, [redacted], is designated by the Sponsor. The Coordinating Investigator is responsible for the overall conduct of the study and signing the Clinical Study Report on behalf of the participating site investigators upon study conclusion.

4.2 Dose Selection Rationale

The selection of doses, dosing interval and duration considered the results of the nonclinical pharmacology, pharmacokinetic and toxicology studies, which are presented in the Investigator's Brochure (IB).

The QD topical application frequency at the proposed concentrations is expected to result in continuous exposure at efficacious levels in a safe range.

4.3 End of Study Definition

The end of the study is defined as the date of the last visit of the last subject in the study globally.

If the Medical Monitor or designee, study monitor, or appropriate regulatory officials indicate that the study should be halted or that a study site should be terminated, this action may be taken after appropriate consultation between NFlection and the appropriate parties. NFlection has the right to terminate this study at any time for any reason.

Conditions that may warrant termination of the study include, but are not limited to:

- The discovery of an unexpected, serious, or unacceptable risk to the subjects enrolled in the study.
- A decision by NFlection to suspend or discontinue testing, evaluation, or development of the product.

4.4 Study Duration

The duration of study participation for each subject is anticipated to be a maximum of 242 days. Including an up to 28-day screening period, a 182-day treatment period and a 28-day no-treatment follow-up period. The last study visit has a window of ±4 days.

The duration of the study from first subject first visit to last subject last visit is planned to be approximately 86 weeks. The study end date is the date of the last subject's last visit.

5 STUDY POPULATION

This study will enroll male and female subjects at least 18 years of age, with a clinical diagnosis of NF1.

5.1 Number of subjects

Approximately 168 subjects will be randomized to 1 of the 3 study medication treatment groups at approximately 27 United States (US) investigational centers with the goal of at least 150 randomized subjects completing the study.

5.2 Study Entry Criteria

5.2.1 Inclusion Criteria

To be eligible to participate in this study at Visit 1, the subject must fulfill all the following criteria:

1. Subject is at least 18 years of age
2. Subject must provide written informed consent prior to any study procedures

3. Subject must have a clinical diagnosis of NF1
4. Subject has 10 clinically diagnosed Target cNFs with preferably 2 Target cNFs located on the face and 8 Target cNFs located on the anterior trunk or upper extremities. Alternatively, at least 1 Target cNF is located on the face, in which case 9 Target cNFs must be located on the anterior trunk or upper extremities. Each Target cNF must meet the following criteria:
    - Has, in the investigator's opinion, a clinically typical appearance
    - Is not within 1 cm of the orbital rim
    - Is not covered with hair that might, in the investigator's opinion, interfere with obtaining photographs or impair evaluation of the cNF
    - Has a Physician's Tumor Assessment grade ≥2
    - Is dome shaped
    - Is not pedunculated
    - Is a discrete cNF surrounded by sufficient non-affected skin that, in the investigator's opinion:
        i. The dimensions can be measured
        ii. The perimeter can be outlined in the study photographs
    - Is not irritated (*e.g.*, bleeding, inflamed)
    - Is not in an area subject to repeated trauma (*e.g.*, area that is shaved, on the beltline, under a bra strap, etc.)
    - Does not have an active cutaneous infection
    - Target cNFs on the face must have the following tumor dimensions:
        i. Has a length that is ≥5mm and ≤14mm
        ii. Has a width that is ≥5mm and ≤14mm
        iii. Has a height that is ≥2mm.
    - Target cNFs on the anterior trunk or upper extremities must have the following tumor dimensions:
        i. Has a length that is ≥7mm and ≤14mm
        ii. Has a width that is ≥5mm and ≤14mm
        iii. Has a height that is ≥2mm
5. Subject agrees to minimize exposure of Target cNFs to sunlight and to use her/his routine sunscreen if exposure cannot be avoided
6. Subject agrees NOT to use tanning beds
7. Subject is willing to forego treatment of each Target cNF, except protocol specified therapy, during the study
8. Female subjects who are women of childbearing potential must have a negative urine pregnancy test result and be willing to use a protocol approved, contraceptive method for the duration of the study
9. Subject is willing and able to follow all study instructions and to attend all study visits.

5.2.2 Exclusion Criteria

A subject who meets any of the following criteria at Visit 1 (except where noted at Visit 2) will be excluded from participation in this study:

1. Subject has used any of the following topical therapies within the specified period prior to Visit 2 on or in proximity to any Target cNF that, in the investigator's opinion, impairs evaluation of any the cNFs or which exposes the subject to an unacceptable risk by study participation:
    - Corticosteroids; 30 days
    - Prescription retinoids (*e.g.*, tazarotene, tretinoin, adapalene); 30 days
    - > 5% of an alpha-hydroxy acid (*e.g.*, glycolic acid, lactic acid); 30 days
    - Fluorouracil; 30 days
    - Imiquimod; 30 days
    - LASER, light (*e.g.,* intense pulsed light [IPL], photo-dynamic therapy [PDT]) or other energy-based therapy; 180 days
    - MEK inhibitor or BRAF inhibitor; ever.
2. The subject has used any of the following systemic medications therapies within the specified period prior to Visit 2:
    - Retinoids (*e.g.*, etretinate, isotretinoin); 90 days
    - MEK inhibitors; 180 days
    - BRAF inhibitors; 180 days
3. Subject has a history of hypersensitivity to any of the ingredients in the study medications
4. Subject has any known intercurrent illness or physical condition that would, in the investigator's opinion, impair evaluation of a Target cNF or which exposes the subject to an unacceptable risk by study participation
5. Subject has, in the investigator's opinion, clinically relevant history of liver disease, including viral hepatitis, current alcohol abuse, or cirrhosis
6. Subject has a history of metastatic disease, or active cancer (excluding non-melanoma skin cancer, Stage I cervical cancer, ductal carcinoma *in situ* of the breast, or Stage 0 chronic lymphocytic lymphoma) within the previous 5 years
7. Subject has any condition (*e.g.*, other skin conditions or diseases, metabolic dysfunction, physical examination findings, clinical laboratory findings) or situation (*e.g.*, vacation, scheduled surgery) that would, in the investigator's opinion, impair evaluation of a Target cNF or which exposes the subject to an unacceptable risk by study participation
8. Subject has participated in an investigational drug trial in which administration of an investigational study medication occurred within the previous 30 days.

5.3 Subject identifier (SI)

At Visit 1 (Screening) the investigator or designee will assign a unique four-digit subject identifier (SI) to each subject.

The SI format will be NN-NN where the first 2 digits are the investigational center site number (using leading zeroes as appropriate) assigned by NFlection. The final 2 digits are the subject

number and must be assigned in ascending numerical order, without omitting or repeating any number, starting with 01 at each investigational center. For example, the SI for the second subject that signs an informed consent at site number 14 would be 14-02.

The subject will be identified using the SI in all study documentation for the duration of the study.

5.4 Subject discontinuation from the study

Subjects will be informed that they are free to withdraw from the study at any time and for any reason.

The investigator may remove a subject from the study if, in the investigator's opinion, it is not in the best interest of the subject to continue the study. The investigator must remove a subject from the study if the subject experiences:

- A Serious Adverse Event the investigator defines as related to the study medication, regardless of the intensity of the event
- A non-serious adverse event the investigator defines as related to study medication that has a severity of severe and requires treatment to resolve.

Examples of other reasons subjects may be discontinued from the study are a change in compliance with an inclusion or exclusion criterion, occurrence of AEs, occurrence of pregnancy or use of a prohibited therapy. Notification of discontinuation will immediately (within 24 hours) be made to the study monitor.

All withdrawn subjects with ongoing AEs will be followed as appropriate.

The study may be discontinued at the discretion of NFlection. Some examples of reasons for discontinuation are the occurrence of the following:

- Increased frequency, severity, or duration of known AEs
- Medical, regulatory, or ethical reasons affecting the continued performance of the study
- Difficulties in the recruitment of subjects.

5.4.1 Screen Failures

A subject who consents to participate in the study but does not complete Visit 1 is considered a screen failure.

A minimal amount of screening failure information is required to ensure appropriate reporting of screen failures and to respond to queries from regulatory authorities. For detailed screening failure requirements please refer to the case report form (CRF) completion guidelines.

Subjects who are screen failures may be scheduled for a second Visit 1 (*i.e.*, rescreened) only after consultation of the Medical Monitor. If the subject will be rescreened, a new SI will be created. A subject may be rescreened only 1 time.

5.4.2 Randomization Failures

A subject who completes Visit 1 and is subsequently not randomized to study medication is considered a randomization failure.

A minimal set of CRFs is required to ensure appropriate reporting of subjects who are randomization failures. Detailed instructions for documenting subjects who are randomization failures will be included in the CRF completion guidelines.

5.4.3 Early Termination Visit

The investigator should complete the following study procedures for randomized subjects who prematurely discontinue from the study:

- For subjects who discontinue from the study prior to Visit 8, complete the Visit 8 procedures
- For subjects who complete Visit 8 and discontinue from the study prior to Visit 9 complete the Visit 9 procedures.

Detailed instructions for documenting subjects who prematurely discontinue from the study will be included in the CRF completion guidelines.

5.4.4 Lost to Follow-up

A subject who repeatedly does not attend scheduled visits and is unable to be contacted by the study site will be considered lost to follow-up.

The following actions for subjects who are lost to follow-up:

- The investigator or designee must attempt to contact the subject and reschedule the missed visit as soon as possible, must counsel the subject on the importance of maintaining the assigned visit schedule and must ascertain whether or not the subject wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the subject. These efforts should include where possible, 2 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods. These contact attempts should be documented in the subject's study file.
- Should the subject continue to be unreachable, she/he will be considered to have withdrawn from the study.

Detailed instructions for documenting subjects who are lost to follow-up will be included in the CRF completion guidelines.

5.5 Previous and Concomitant Therapies

5.5.1 Previous therapies

At Visit 1 and Visit 2, the investigator or designee will question the subject to ensure they have not used any excluded therapies.

5.5.2 Concomitant Therapies

Concomitant therapies are any new or existing therapy received from Visit 1 until discharge from the study.

Concomitant therapies include drug (*e.g.*, prescription, over-the-counter) and non-drug (*e.g.*, chiropractic, physical therapy, energy-based treatments) therapies. Subjects will refrain from receipt of any therapy in compliance with the inclusion/exclusion criteria and prohibited therapies (Section 5.5.3). Subjects should refrain from changing the use of any concomitant therapies during the study.

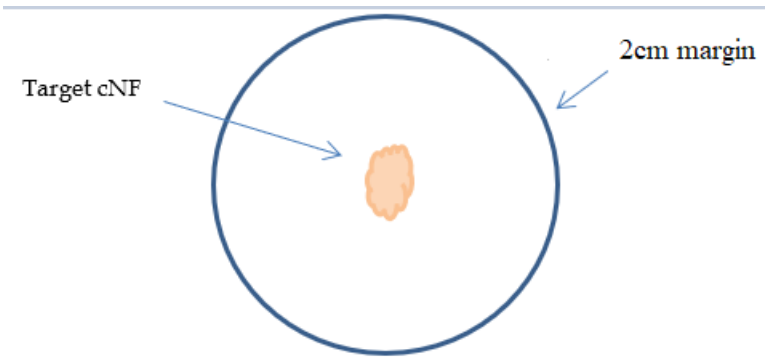
Any new or modified concomitant therapy must be recorded and considered to determine if it is related to an AE. An AE must be reported unless the therapy is modified for non-medical reasons *(e.g.*, health insurance purposes) or it is for prophylaxis (*e.g.,* vaccinations).

Do not report "PRN" (*i.e.*, as needed) as the frequency for a concomitant therapy. Report each time the therapy is used with a start date, end date and frequency.

5.5.3 Prohibited therapies

Subjects must not use any systemic therapy for cNF and must not use any topical cNF therapy on any Target cNF.

During this study, subjects are prohibited from using therapies listed in the exclusion criteria. Topical corticosteroids are not allowed to treat Target cNFs or within a 2cm margin of a Target cNF but may be used on non-Target cNF areas after consultation with and approval from the Medical Monitor (diagram not to scale).



The investigator should notify the Medical Monitor and the study monitor immediately (within 24 hours) if any prohibited therapies are required to ensure subject safety.

Subjects must avoid applying any topical product to any Target cNF for at least 6 hours after any study medication application.

5.6 Study Medications

The study medications are faint yellow, clear gels and are indistinguishable in physical appearance. Study medications must be maintained in a secure area with limited access under appropriately controlled and monitored storage conditions at each investigational center.

5.6.1 Study medication identity

Study Medication Information			
Name	NFX-179 Gel [redacted]	NFX-179 Gel [redacted]	NFX-179 Gel Vehicle
Manufacturer	MedPharm Limited Unit 1, Chancellor Court, 50 Occam Road, Surrey Research Park Guildford, Surrey GU2 7AB United Kingdom		
Active ingredient	[redacted]		None
Active concentration	[redacted]	[redacted]	0%
Storage conditions	59°F to 77°F (15°C to 25°C)		

The investigator or designee must confirm appropriate storage temperature was maintained during shipment for all study medication received and any discrepancies must be reported to NFlection and resolved before the study medication is dispensed.

5.6.2 Study medication packaging and labeling

The study medications will be packaged in identical appearing white glaminate tubes that each contain [redacted] (g) of study medication.

One Subject Kit that contains 5 tubes of study medication in two separate cartons of 3 and 2 tubes, respectively, will be prepared for each subject.

At a minimum, each carton will be labeled with a two-part, three-panel label. One part of the label remains affixed to the Subject Kit and the second part, a two-panel tear-off, is separated when the Subject Kit is first dispensed to the subject. The affixed label part and the first panel of the tear-off label part show at least the following:

- Subject Kit number (Subject Kit number is also the randomization number)
- Protocol number
- Space to enter the SI
- Space to enter the date randomized
- Storage conditions
- NFlection information.

The second panel of the tear-off part is a blinded label (*e.g.*, scratch-off panel or equivalent) which when opened identifies the study medication in the Subject Kit. The blinded label should be opened only in a medical emergency.

At a minimum, study medication tubes will be labeled with a one-part label that remains attached to the tube and shows at least the following:

- Subject Kit number
- Protocol number
- Tube number
- Space to enter the SI
- Space to enter the date dispensed
- Directions for use
- Investigational drug warning.

5.6.3 Method of study medication assignment

Prior to the study start NFlection, or a designated third party, will generate a list of randomization numbers that will be provided to the assigned vendor for study medication labeling. The randomization number is also the Subject Kit number.

The randomization list will be stored with access limited to the appropriate personnel for the study medication labeling. The randomization list will be made available as appropriate to unblind the database.

5.6.4 Subject randomization

At Visit 2, the investigator will determine the subject's eligibility for randomization to study medication. To be eligible for randomization the subject must:

- Have a PTA ≥2 for all Target cNFs
- Have clinical laboratory test results for all measured analytes at Visit 1 and all results are either within the range of normal for the laboratory or, any abnormal results, are defined as Not Clinically Relevant (NCR) by the investigator.
- Have, if a Woman of Childbearing Potential (WOCBP), a negative urine pregnancy test result at Visit 2.
- Have NOT used any topical or system therapies within the specified period prior to Visit 2 per the exclusion criteria

The investigator or designee will assign study medication to eligible subjects by selecting the

Subject Kits in chronological sequence in ascending numerical order starting with the lowest available Subject Kit number. The investigator will not omit or reuse any Subject Kit number.

5.6.5 Dispensing and collecting study medication

The study medication must be dispensed only to study subjects, only at investigational centers specified on the Form FDA 1572 (or its equivalent) and only by authorized personnel as required by applicable regulations and guidelines.

At Visit 2, after a subject is randomized, locate the Subject Kit with the lowest available number and complete the label. Next locate the unused study medication tube with the lowest available number and complete the label. Weigh the study medication tube. Dispense one study medication tube to the subject. Observe the subject apply a thin layer of study medication to each cNF tumor. Weigh the study medication tube post subject application of study medication.

At Visits 3-7, examine the study medication tube(s) dispensed to the subject, weigh the tube(s), return tubes that contain, in the investigational staff member's opinion, useable study medication to the subject and collect tubes that contain no useable study medication. Dispense a new tube of study medication, if required for treatment until the next visit, following the instructions above. A subject should not possess more than 2 tubes of study medication at one time.

At Visit 8, collect all study medication tubes from the subject and weigh each tube.

The subject must bring all dispensed study medication tubes with them to all visits.

The investigational center staff member should make every effort to obtain all dispensed and unused study medication. Two documented telephone contacts followed by a registered letter to the subject are adequate follow-up efforts. If these efforts fail, the reason for the failure must be noted on the appropriate line of the study medication inventory CRF.

All unused and un-dispensed study medication should be held for inspection by NFlection's study monitor. Upon completion of the study all study medication will be returned to NFlection or a designated third party by the study monitor using a traceable method unless returned study

medication is destroyed by the site according to applicable SOP.

5.6.6 Weighing study medication

An investigational center staff member will weigh each study medication tube when dispensed, at each study visit, and when returned using the provided scale (or equivalent). The study medication container weight must be reported to the nearest 0.1 g. The study medication tubes must be weighed with the label attached and the cap on and without any other packaging.

At Visit 2, the study medication tube dispensed to the subject must be weighed pre subject application of study medication and post subject application of study medication.

The scale used to weigh the study medication tubes must be calibrated, according to the instructions provided for the scale, and the calibration documented, each day the scale is used, prior to use. Any scale that does not pass the calibration test must not be used to weigh the study medication.

5.6.7 Route of Administration, frequency and treatment period

The study medications are applied topically to each Target cNF, once daily for 182 days (26 weeks).

5.6.8 Study medication application

The study medications are for external, topical use on each Target cNF only and on the appropriate study subject only.

To perform a study medication application the subject should:

- Wash her/his hands before starting the application
- Avoid applying the study medication to any open wounds or obviously infected skin
- Apply an amount of the assigned study medication sufficient to cover each Target cNF with a thin layer of the study medication
- Gently rub in the study medication until no visible accumulation is evident
- Wash her/his hands after completing the application.

The subject must apply study medication to the entire area of each Target cNF limiting exposure to the un-affected skin surrounding the cNF.

At Visit 2, an investigational center staff member will instruct the subject on the proper application technique and observe the subject's study medication application to ensure proper

application technique and record the time the subject completes the application to the last Target cNF as the Application Completion Time. A staff member will monitor the subject for adverse events for at least 20 minutes after the Application Completion Time.

Subjects should continue QD application of the assigned study medication to each Target cNF for 182 days (26 weeks) with 18-30 hours between applications.

Subjects should not apply the study medication within 6 hours prior to a study visit, except on Visit 4 when the subject should apply study medication 4 (± 2 hours) prior to the scheduled appointment time. Record the study medication application time on the day of Visit 4.

If during the treatment phase a Target cNF clears (*i.e.*, PTA grade of 0) instruct the subject to continue QD application to the area of the cNF for the remainder of the treatment period.

After completing a study medication application, a subject should not:

- Wash or submerse any Target cNF for at least 6 hours
- Apply any topical products (*e.g.*, cosmetics, emollient/moisturizer, sunscreens) to any Target cNF for at least 6 hours.

At Visits 3-7 review the application technique with the subject to ensure they are performing the application properly, are using an appropriate amount of study medication and are applying the study medication to the correct cNFs.

5.6.9 Dose Modification

Subjects should not modify the study medication application procedure or frequency unless instructed to do so by the investigator. All application modifications must be reported on the appropriate CRF page.

If any significant study medication intolerance or safety issue occurs, after consulting with the Medical Monitor, the investigator or designee may direct the subject to reduce the study medication application frequency. If the subject cannot perform QD applications to a specific Target cNF(s), the subject may continue study medication treatment of <10 Target cNFs selected by the investigator for the duration of the study after consultation and approval from the Medical Monitor. If the subject cannot perform QD applications to any Target cNF for a total of 25 days,

the subject must be removed from the study. The total of 25 days applies to individual Target cNFs and is not an aggregate of non-treatment days of each Target cNF. Each Target cNF that meets or exceeds 25 total days of non-treatment cannot restart treatment. All 10 Target cNFs must be evaluated at each visit per protocol requirements regardless of study medication application frequency.

5.6.10 Accountability

The investigator or designee will maintain an accurate record of the receipt of the study medications as shipped by NFlection or designee, including the date received and the condition of the study medications. One copy of this receipt will be returned to NFlection when the contents of the study medication shipment have been verified and one copy maintained in the study file. In addition, an accurate study medication disposition record will be kept, specifying the amount dispensed to each subject and the date of dispensing. This inventory record will be available for inspection at any time. At the completion of the study, the original inventory record will be available for review by NFlection upon request.

5.6.11 Return and disposition of study medication

At the completion of the study, all unused study medication will be returned to NFlection or designee for disposal per NFlection or designee's written instructions unless returned study medication is destroyed by the site according to applicable SOP.

5.7 Blinding

5.7.1 Verification of blinding

Blinding of the study medications is important for validity of this study. This study uses a double-blind design. The study medications are indistinguishable in appearance, packaging and labeling.

5.7.2 Unblinding the study medication

Blinding is important for validity of this study; however, the blind may be broken in the event of a medical emergency in which knowledge of the study medication identity is critical to the management of the subject's course of treatment. Before breaking the blind, the investigator should determine that the information is necessary (*i.e.*, that it will alter the subject's immediate course of treatment). In many cases, particularly when the emergency is clearly not study

medication-related, the problem may be effectively managed by assuming that the subject is receiving active study medication without the need for unblinding.
If deemed necessary to break the blind for a study subject, attempt to contact the Medical Monitor to obtain concurrence. If it is not possible to contact the Medical Monitor beforehand, contact her/him as soon as possible after breaking the blind for a subject.

To identify a subject's study medication, locate the second panel of the Subject Kit tear-off label attached to the subject's CRF and follow the unblinding instructions on the label. Record the date of unblinding, the reason for unblinding and the initials of the investigational center staff member who performed the unblinding in the subject's CRF.

Any subject whose blind has been broken must be discharged from the study.

5.8 Study medication adherence

Adherence with the study medication application frequency and application of an appropriate amount of study medication will be monitored by questioning the subject regarding adherence at each visit and by measuring the weight of the study medication tubes when dispensed to the subject, at each treatment period visit and when collected from the subject.

5.9 Subject instructions

At Visit 1, an investigational center staff member will dispense a Subject Instruction sheet to each subject.

During the entire duration of the study subjects must:

- Continue to use her/his routine cleansers and cosmetics
- Not apply any topical products, including the study medication to any Target cNF within 6 hours prior to a study visit
- Minimize exposure of Target cNFs to sunlight and use her/his routine sunscreen if exposure cannot be avoided
- Not use tanning beds
- Bring the subject instruction sheet to every visit.

During the 182-day (26-week) treatment period, subjects must:

- Apply the study medication to each Target cNF as directed, once daily, with 18-30 hours between applications

- Not apply the study medication to any open wounds or obviously infected skin
- Not wash or submerge any Target cNF for at least 6 hours after a study medication application
- Not apply the study medication, to any Target cNF within 6 hours prior to a study visit, , except on Visit 4 when the subject should apply study medication 4 (± 2 hours) prior to the scheduled appointment time.
- Not apply any topical products to any Target cNF within 6 hours prior to a study visit
- Not apply any topical products to any Target cNF for at least 6 hours after a study medication application
- Not allow anyone else to use your study medication
- Keep the study medication away from children
- Store the study medication at room temperature
- Bring all study medication tubes to every visit.

5.10 Other study supplies

In addition to the equipment and supplies provided for performing study procedures, such as blood sampling, urine pregnancy tests and photography, NFlection, or designee, will provide the following items to each investigational center prior to the initiation of subject enrollment:

- Rulers for measuring each Target cNF
- Scales for weighing the study medication tubes.

6 STUDY VISITS AND PROCEDURES

6.1 Schedule of Events

Visit	1 Screening	2 Baseline	3	4	5	6	7	8	9	Protocol Section
Day	**-28 to 0**	**1**	**8**	**29**	**57**	**85**	**141**	**183**	**211**	
Week	**-4**	**0**	**1**	**4**	**8**	**12**	**20**	**26**	**30**	
Screening period	↔									
QD Treatment period		↔	↔	↔	↔	↔	↔	↔		
No treatment follow-up period									↔	
Informed consent	X									12.3
Inclusion/exclusion criteria	X[1]	X								5.2
Demographics	X									7.3.1
Medical history	X[1]	X								7.1.4
Physical examination	X									7.1.5
Vital signs	X[1]	X						X	X	7.1.6
Clinical laboratory samples	X[1]	X[2]		X				X		7.1.2
Pharmacokinetic samples				X						7.3.2
Urine pregnancy test	X[1]	X		X	X	X	X	X	X	7.1.7
Target cNF identification	X[1]	X	X	X	X	X	X	X	X	6.3
Local tolerability assessment (LTA)		X	X	X	X	X	X	X	X	7.1.3
Target cNF dimensions	X[1]	X		X	X	X	X	X	X	7.2.1
Physician's tumor assessment (PTA)	X[1]	X		X	X	X	X	X	X	7.2.2
Subject's self-assessment (SSA)		X		X	X	X	X	X	X	7.2.3
Patient reported outcome measure (PROM)		X				X		X		7.3.3
Standardized photography	X[1]	X				X		X	X	7.3.4
Subject randomization		X								5.6.4
Weigh study medication		X	X	X	X	X	X	X		5.6.6
Dispense/collect study medication		X	X	X	X	X	X	X		5.6.5
Subject instructions	X[1]	X	X	X	X	X	X	X	X	5.9
Dispense body charts	X[1]	X								6.3
Concomitant therapies	X[1]	X	X	X	X	X	X	X	X	5.5
Adverse events		X	X	X	X	X	X	X	X	8

1. May be combined with Visit 2
2. May be performed locally in addition to central lab sample collection ONLY IF Visits 1 and 2 are combined

6.2 Study Visits

A written, signed informed consent form (ICF) must be obtained from each subject prior to performing any study related procedures and/or evaluations.

6.2.1 Visit 1/Day -28 to 0/Week -4 to 0 (Screening)

At Visit 1, the investigator or designee will:

1. Review and explain the nature of the study to the subject, obtain the subject's signature on the appropriate approved ICF and Health Insurance Portability and Accountability Act (HIPAA) authorization and provide a signed and dated copy to the subject
2. Assign a Subject Identifier to the subject
3. Confirm the subject meets all inclusion criteria and no exclusion criteria
4. Collect demographic and medical history information
5. Report concomitant therapies information
6. Conduct a physical examination
7. Measure vital signs
8. Collect samples for clinical laboratory tests
9. Perform a urine pregnancy test for WOCBP
10. Identify 10 clinically diagnosed Target cNFs (preferably 2 Target cNFs located on the face and 8 Target cNFs are located on the anterior trunk or upper extremities. Alternatively, at least 1 Target cNF is located on the face, in which case 9 Target cNFs must be located on the anterior trunk or upper extremities)
11. Create Visit 1 body charts and dispense a photocopy to the subject
12. Perform a Physician's Tumor Assessment (PTA) on each Target cNF and confirm each meets the enrollment criteria
13. Measure the dimensions of each Target cNF and confirm each meets the enrollment criteria
14. Take standardized photographs of each Target cNF
15. Review the study instructions with the subject and dispense a Subject Instruction Sheet
16. Schedule Visit 2.

6.2.2 Visit 2/Day 1/Week 0 (Randomization; start of QD treatment)

Visit 2 must occur within 28 days (4 weeks) after Visit 1.

Subsequent study visit dates must be scheduled based on the date of this visit.

This visit may be combined with Visit 1 and only with advance Sponsor approval. If combined with Visit 1, central laboratory samples must be collected along with local laboratory samples. Randomization must not occur until the investigator reviews the subject's Visit 1 clinical laboratory test results or local laboratory test results, if applicable.

At this visit, the investigator or designee will perform the following procedures PRIOR TO RANDOMIZATION:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report any changes as medical history

2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes as appropriate
3. Confirm the subject meets all inclusion criteria and no exclusion criteria
4. Confirm the subject has followed all study instructions
5. Perform a urine pregnancy test for WOCBP
6. Collect Visit 1 body charts
7. Create Visit 2 body charts and dispense a photocopy to the subject
8. Confirm the location of each Target cNF identified
9. Measure the dimensions of each Target cNF
10. Have the subject perform a Subject's Self-Assessment (SSA) for each Target cNF
11. Perform a PTA for each Target cNF
12. Confirm subject is eligible for randomization, discharge subjects who are not eligible from the study.

Determine the subject's eligibility for randomization. Ineligible subjects must be discontinued from the study. For eligible subjects the investigator or designee will perform the following procedures:

1. Have the subject perform a pre-application Local Tolerability Assessment (LTA) of the symptoms for each Target cNF
2. Have the subject perform a Patient Reported Outcome Measure (PROM) for each Target cNF
3. The investigator will perform a pre-application LTA of the signs for each Target cNF
4. Take standardized photographs of each Target cNF
5. Measure vital signs
6. Collect samples for clinical laboratory tests
7. Randomize eligible subjects
8. Weigh study medication tube pre first study medication application and record weight
9. An investigational center staff member must:
    - Instruct the subject on the proper study medication application technique
    - Observe the subject's first study medication application to each Target cNF and record the Application Completion Time
    - Weigh the study medication tube POST first study medication application and record weight
    - Dispense study medication
    - Monitor the subject for adverse events for at least 20 minutes after the Application Completion Time
10. Have the subject perform a post-application LTA of the symptoms for each Target cNF 10 (±4) minutes after the Application Completion Time
11. The investigator will perform a post-application LTA of the signs for each Target cNF 20 (±4) minutes after the Application Completion Time
12. Review the study instructions with the subject
13. Schedule Visit 3.

6.2.3 Visit 3/Day 8/Week 1: 7(±4 days) after Visit 2 (QD treatment)

Subjects should not apply the study medication within 6 hours prior to these visits.

At Visit 3, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs as appropriate
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes as appropriate
3. Confirm the subject has followed all study instructions
4. Confirm the location of each Target cNF
5. Have the subject perform an LTA of the symptoms for each Target cNF
6. The investigator will perform an LTA of the signs for each Target cNF
7. Weigh study medication
8. Collect and dispense study medication as appropriate
9. Review the study instructions, including application technique and Target cNF locations, with the subject
10. Schedule the next study visit.
11. Remind subject to apply study medication 4 (±2) hours prior to Visit 4

6.2.4 Visit 4/Day 29/Week 4: 28 (±4 days) after Visit 2 (QD treatment)

Only at selects sites participating in Pharmacokinetic sampling: At Visit 4, subjects must apply the study medication 4 (±2) hours prior to this visit.

At sites NOT participating in Pharmacokinetic sampling: At Visit 4, subjects should not apply the study medication within 6 hours prior to this visit.

At Visit 4, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs as appropriate
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes as appropriate
3. Confirm the subject has followed all study instructions
4. Collect samples for clinical laboratory tests and pharmacokinetics
5. Record date and time of last study medication application
6. Record 24-hour time of pharmacokinetic sample collection
7. Perform a urine pregnancy test for WOCBP
8. Confirm the location of each Target cNF
9. **FOR EACH TARGET cNF**:
    - Perform a PTA
    - Have the subject perform an SSA
    - Measure the dimensions
10. Have the subject perform an LTA of the symptoms for each Target cNF
11. The investigator will perform an LTA of the signs for each Target cNF
12. Weigh study medication
13. Collect and dispense study medication as appropriate
14. Review the study instructions, including application technique and Target cNF locations, with the subject
15. Schedule the next study visit.

6.2.5 Visit 5/Day 57/Week 8: 56 (±4 days) after Visit 2 (QD treatment)

Subjects should not apply the study medication within 6 hours prior to this visit.

At Visit 5, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs as appropriate
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes as appropriate
3. Confirm the subject has followed all study instructions
4. Perform a urine pregnancy test for WOCBP
5. Confirm the location of each Target cNF
6. **FOR EACH TARGET cNF**:
    - Perform a PTA
    - Have the subject perform an SSA
    - Measure the dimensions
7. Have the subject perform an LTA of the symptoms for each Target cNF
8. The investigator will perform an LTA of the signs for each Target cNF
9. Weigh study medication
10. Collect and dispense study medication as appropriate
11. Review the study instructions, including application technique and Target cNF locations, with the subject
12. Schedule the next study visit.

6.2.6 Visit 6/Day 85/Week 12: 84 (±4 days) after Visit 2 (QD treatment)

Subjects should not apply the study medication within 6 hours prior to this study visit.

At Visit 6, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs as appropriate
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes as appropriate
3. Confirm the subject has followed all study instructions
4. Perform a urine pregnancy test for WOCBP
5. Confirm the location of each Target cNF
6. Perform a PTA for each Target cNF
7. Have the subject perform a SSA for each Target cNF
8. Have the subject perform a PROM for each Target cNF
9. Have the subject perform an LTA of the symptoms for each Target cNF
10. The investigator will perform an LTA of the signs for each Target cNF
11. Measure the dimensions of each Target cNF
12. Take standardized photographs of each Target cNF
13. Weigh study medication
14. Collect and dispense study medication as appropriate
15. Review the study instructions, including application technique and Target cNF locations, with the subject

16. Schedule the next study visit.

6.2.7 Visit 7/Day 141/Week 20: 140 (±4 days) after Visit 2 (QD treatment)

Subjects should not apply the study medication within 6 hours prior to this visit.

At Visit 7, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs as appropriate
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes as appropriate
3. Confirm the subject has followed all study instructions
4. Perform a urine pregnancy test for WOCBP
5. Confirm the location of each Target cNF
6. **FOR EACH TARGET cNF**:
    - Perform a PTA
    - Have the subject perform an SSA
    - Measure the dimensions
7. Have the subject perform an LTA of the symptoms for each Target cNF
8. The investigator will perform an LTA of the signs for each Target cNF
9. Weigh study medication
10. Collect and dispense study medication as appropriate
11. Review the study instructions, including application technique and Target cNF locations, with the subject
12. Schedule the next study visit.

6.2.8 Visit 8/Day 183/Week 26 (End of QD treatment; start of no treatment follow-up; early termination if subject discontinues from the study prior to Visit 8)

This visit must occur 182 days (±4 days) after Visit 2.

Subjects should not apply the study medication within 6 hours prior to this study visit.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs as appropriate
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes as appropriate
3. Confirm the subject has followed all study instructions
4. Measure vital signs
5. Collect samples for clinical laboratory tests
6. Perform a urine pregnancy test for WOCBP
7. Confirm the location of each Target cNF
8. Perform a PTA for each Target cNF
9. Have the subject perform a SSA for each Target cNF
10. Have the subject perform a PROM for each Target cNF
11. Have the subject perform an LTA of the symptoms for each Target cNF
12. The investigator will perform an LTA of the signs for each Target cNF

13. Measure the dimensions of each Target cNF
14. Take standardized photographs of each Target cNF
15. Weigh study medication
16. Collect all study medication
17. Review the study instructions with the subject. If the subject wishes to be contacted about participation in the exit interview study inform the identified individual at the exit interview vendor that the subject has completed study participation and provide them with the subject's contact information
18. Schedule the next study visit.

6.2.9 Visit 9/Day 211/Week 30 (End of study, early termination if subject completes Visit 8 and discontinues from the study prior to Visit 9)

This visit must occur 210 days (±4 days) after Visit 2.

At this visit, the investigator or designee will perform the following procedures:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs as appropriate
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes as appropriate
3. Confirm the subject has followed all study instructions
4. Measure vital signs
5. Perform a urine pregnancy test for WOCBP
6. Confirm the location of each Target cNF
7. Have the subject perform an LTA of the symptoms for each Target cNF
8. The investigator will perform an LTA of the signs for each Target cNF
9. Measure the dimensions of each Target cNF
10. Take standardized photographs of each Target cNF
11. Perform a PTA for each Target cNF
12. Have the subject perform a SSA for each Target cNF
13. Discharge the subject from the study.

6.2.10 Unscheduled Visit

The investigator may see a subject for an unscheduled study visit at any time it is necessary, in the investigator's opinion.

At unscheduled visits, the investigator or designee will perform the following procedures, at a minimum:

1. Query the subject in a non-directive manner about any changes in her/his health since the previous visit and report all AEs as appropriate
2. Query the subject about any changes in her/his concomitant therapies since the previous visit and report changes as appropriate
3. Review the study instructions with the subject
4. Schedule the next study visit.

Complete other study procedures that are, in the investigator's opinion, appropriate for the visit. Detailed instructions for documenting unscheduled visits will be included in the CRF completion guidelines.

6.3 Target cNF identification

At Visit 1 the investigator will identify 10 clinically diagnosed Target cNFs. Preferably 2 Target cNFs are located on the face and 8 Target cNFs are located on the anterior trunk or upper extremities. Alternatively, at least 1 Target cNF is located on the face, in which case 9 Target cNFs must be located on the anterior trunk or upper extremities.

For this study, the face, anterior trunk, and upper extremities are defined as follows:

- Face:
  - Vertically from the mandibular ridge to the hairline (for subjects with a receding hair the hairline is defined by a vertical lie drawn coronally from tragus to tragus)
  - Horizontally from tragus to tragus, excluding the eyelids, eyebrows, and areas within 1 cm of the orbital rim.
- Anterior trunk:
  - The front of the torso down to the beltline, excluding the neck
- Upper extremities:
  - Arms from the shoulders to the wrist, (excluding the hands).

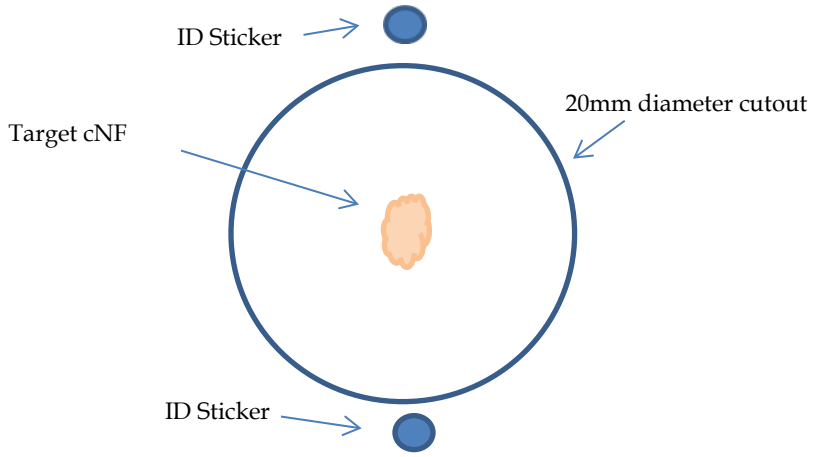
At Visit 1 each of the 10 clinically diagnosed Target cNFs must meet the following criteria for the subject to be enrolled:

- Has, in the investigator's opinion, a clinically typical appearance
- Is not within 1 cm of the orbital rim

- Is not covered with hair that might, in the investigator's opinion, interfere with obtaining photographs or impair evaluation of the cNF
- Has a PTA grade ≥2
- Is dome shaped
- Is not pedunculated
- Is a discrete cNF surrounded by sufficient non-affected skin that, in the investigator's opinion:
    i. The dimensions can be measured
    ii. The perimeter can be outlined in the study photographs
- Is not irritated (*e.g.*, bleeding, inflamed)
- Is not in an area subject to repeated trauma (*e.g.*, on the beltline, under a bra strap, etc.)
- Does not have an active cutaneous infection
- Target cNFs on the anterior trunk or upper extremities must have the following tumor dimensions:
    i. Has a length that is ≥7mm and ≤14mm
    ii. Has a width that is ≥5mm and ≤14mm
    iii. Has a height that is ≥2mm.
- Target cNFs on the face must have the following tumor dimensions:
    i. Has a length that is ≥5mm and ≤14mm
    ii. Has a width that is ≥5mm and ≤14mm
    iii. Has a height that is ≥2mm

Number the Target cNFs at Visit 1 starting with 1 and proceeding up to 10 with no number omitted or reused. Target cNFs 1 and 2 must be on the face and Target cNFs 3-10 must be on the anterior trunk or upper extremities. If only 1 Target cNF is identified on the face, Target cNF 1 must be on the face and Target cNFs 2-10 must be on the anterior trunk or upper extremities.

For identification in the study photographs with the Target cNF centered in the large template cutout place 2 appropriately numbered Identification (ID) stickers in the small template cutouts (diagram not to scale):



Write the Target cNF Number on at least one ID sticker. Both ID stickers must be visible in the photographs.

The investigator will document the location of each Target cNF on the Visit 1 body charts using the following process:

- Make a circle or similar mark identifying the location of each Target cNF
- Write the Target cNF Number adjacent to the mark
- Also report at least the following additional information on the body charts:
  - Protocol number
  - Subject Identifier.

At Visit 1 and Visit 2, the investigator or designee will dispense a photocopy of the body charts to the subject. New, eligible Target cNF(s) may be selected at Visit 2 if necessary. The investigator or designee will place the original Visit 1 and Visit 2 body charts in the subject's study file.

The investigator or designee must report the approximate location of each Target cNF identified at Visit 1 in the CRFs and include the Target cNF Number.

At Visit 2, the investigator will use the Visit 1 body charts and photographs to identify the location of the 10 Target cNFs identified at Visit 1. If the 10 Target cNFs identified at Visit 1 don't meet eligibility criteria, new eligible Target cNF(s) may be selected at Visit 2.

At Visits 3-9, prior to any Target cNF assessments, an investigational center staff member other than the evaluating investigator will use the Visit 2 body charts and study photographs to identify the location each Target cNF for the study evaluations. A staff member will use the cNF template, center each Target cNF in the large circular cutout and place the 2 ID stickers, numbered as appropriate on the subject's skin.

The investigator is not allowed to participate in the photography process or to use the study photographs to assist with any Target cNF evaluations EXCEPT as noted below:

> **The investigator may view the Visit 2 photographs, and only the Visit 2 photographs, to assist with determining the location of the Target cNFs at Visits 3-9 only if there is no other option to locate the cNFs. If the investigator views the Visit 2 photographs the details of the situation must be reported in the subject's study file and on the CRFs.**

7 STUDY ASSESSMENTS

The study assessments will be performed according to the schedules noted below by the investigator, an appropriately trained investigational center staff member or the subject as noted for each assessment. **The same staff member should perform the assessments for a given subject throughout the study**. If this becomes impossible, appropriate designee with overlapping experience with the study and the subject should perform the assessments.

7.1 Safety assessments

7.1.1 Adverse Event Assessments

Information regarding occurrence of AEs will be captured throughout the study. The study site visits are designed to ensure any untoward events in subjects are quickly identified by the investigator and can be treated promptly. Duration, severity/grade, outcome, treatment, and relationship to study medication will be recorded.

7.1.2 Clinical Laboratory Evaluations

At Visits 1, 2 (prior to the randomization), 4 and 8, a qualified investigational center staff member will collect non-fasting blood and urine samples for clinical laboratory analysis. The following tests, at a minimum, will be conducted:

Chemistry Panel
Albumin
Alkaline phosphatase
Alanine aminotransferase (ALT)
Aspartate aminotransferase (AST)
Blood urea nitrogen (BUN)
Bicarbonate
Calcium
Chloride
Creatinine
Glucose
Lactate dehydrogenase (LDH)
Phosphorus
Potassium
Sodium
Total bilirubin
Total protein
Uric acid

Complete Blood Count
Hematocrit
Hemoglobin
Platelet count
Red blood cell morphology
Red blood cell count
White blood cell count
White blood cell differential
- % & absolute
- Basophils
- Eosinophils
- Lymphocytes
- Monocytes
- Neutrophils

Urinalysis with Microscopic

The results of the clinical laboratory analysis will be reported on the laboratory's standard reports. The investigator must note NCR or clinically relevant (CR) to define the clinical relevance of any result that is outside the normal range for the laboratory. The investigator must date and sign/initial every laboratory report.

The investigator must review each subject's Visit 1 laboratory reports prior to Visit 2. The subject must not be randomized if any of the Visit 1 results are outside normal range for the laboratory AND, in the opinion of the investigator, CR. The investigator must review all laboratory reports in a timely manner.

The investigator must report all laboratory results that are BOTH outside the normal range for the laboratory AND, in the opinion of the investigator, CR as medical history if found prior to the first study medication application or as an AE if found after the first study medication application begins.

The total number of venipunctures and the total volume of blood collected during the study will be limited to that need for the safety monitoring. Refer to the laboratory manual(s) for the collection procedures and the total volume of blood collected.

7.1.3 Local Tolerability Assessment (LTA)

At Visits 2-9, the investigator and the subject will evaluate the signs and symptoms of irritation on each Target cNF using the LTA.

The LTA is the investigator's and the subject's assessment of the average overall severity of the signs and symptoms, respectively, associated with irritation on each Target cNF. The investigator and subject must NOT refer to any other evaluation to assist with these assessments. This is not a comparison with the assessment at any other time point.

The investigator will perform the LTA for signs using the scales below:

Erythema		
0	None	No erythema present
1	Mild	Slight red coloration
2	Moderate	Definite redness
3	Severe	Marked erythema, bright red to dusky dark red in color

Edema		
0	None	No edema
1	Mild	Slight, but definite edema
2	Moderate	Definite edema
3	Severe	Marked edema

Scabbing/Crusting		
0	None	No scabbing/crusting
1	Mild	Slight, but definite scabbing/crusting
2	Moderate	Definite scabbing/crusting
3	Severe	Marked scabbing/crusting

Vesiculation		
0	None	No vesicles
1	Mild	Small vesicles, no pustules
2	Moderate	Vesicles with pustules, transudate may be present
3	Severe	Pustules with transudate, vesicles may be present, may extend outside treatment area

Erosion		
0	None	No erosions
1	Mild	Slight erosion on treatment area
2	Moderate	Obvious erosion(s) on the treatment area
3	Severe	Marked erosion that may extend outside treatment area

The subject will perform the LTA for symptoms using the scales below:

Stinging		
0	None	No stinging
1	Mild	Slight stinging that is not bothersome
2	Moderate	Definite stinging that is somewhat bothersome
3	Severe	Intense stinging that causes definite discomfort and may interrupt daily activities and/or sleep

Burning		
0	None	No burning
1	Mild	Slight burning that is not bothersome
2	Moderate	Definite burning that is somewhat bothersome
3	Severe	Hot burning that causes definite discomfort and may interrupt daily activities and/or sleep

Itching		
0	None	No itching
1	Mild	Slight itching that is noticeable but not bothersome
2	Moderate	Definite itching that is bothersome but does not disrupt activities and/or sleep
3	Severe	Intense itching that is bothersome and may interrupt daily activities and/or sleep

The investigator will perform the LTA for signs for each Target cNF according to the following schedule:

- At Visit 2, when the first study medication application is performed by the subject at the investigational center, perform the LTA for each sign prior to the start of the study medication applications and 20 (±4) minutes after the Application Completion Time.
- At Visits 3-9, the LTA can be performed anytime during the visit.

The subject will perform the LTA for symptoms for each Target cNF according to the following schedule:

- At Visit 2, when the first study medication application is performed by the subject at the investigational center, perform the LTA for each symptom prior to the start of the study medication applications and 10 (±4) minutes after the Application Completion Time
- At Visits 3-9, assess LTA for each symptom over the previous 24 hours anytime during the visit.

To have the subject perform the LTA an investigational center staff member other than the investigator will complete the header on the LTA Scoring Report, provide the report to the subject and identify the first Target cNF to be evaluated. The staff member will identify the Target cNFs by Target cNF ID number, in ascending numerical order starting with the lowest available number. The staff member will then instruct the subject to perform the LTA for the first Target cNF using the scales below. This process of the staff member identifying a Target cNF and the subject performing the LTA will continue until the subject has performed the LTA for each of their Target cNFs.

The subject will be allowed to take as much time as needed to complete the LTA.
The staff member must not influence the subject's assessment, explain the grades, or grade descriptors or in any way assist the subject with the LTA evaluations.

Both the subject and the staff member must initial and date the LTA Scoring Report to indicate that the evaluation was completed as instructed.

The staff member will collect the LTA Scoring Report and maintain it as a source document.

7.1.4 Medical history

At Visit 1, the investigator or designee, for each subject will report medical history including all medical conditions and disease states that:

- Are ongoing
- Require concomitant therapy
- Are, in the investigator's opinion, relevant to the subject's study participation.

Report medical history information for both NF1 and for cutaneous neurofibromas as separate entries. At Visit 2, prior to randomization, the investigator will update the subject's medical history.

7.1.5 Physical Examination

At Visit 1, the investigator or designee will perform a complete physical examination for the subject that will include, at a minimum, the following body systems, and organs:

- General appearance
- HEENT (Head, eyes, ears, nose, and throat)
- Respiratory
- Cardiovascular
- Abdominal
- Extremities
- Musculoskeletal
- Lymphatic
- Skin:
    - Report cNFs as abnormal and clinically significant as part of the documentation of the physical examination.
- Neurological:
    - Report *NF1* as abnormal and clinically significant as part of the documentation of the physical examination.
- Gastrointestinal.

7.1.6 Vital Signs

At Visits 1, 2 (prior to the randomization), 8 and 9, a qualified investigational center staff member will measure the following vital signs for each subject:

- Body temperature
- Pulse rate
- Respiration rate
- Blood pressure (systolic and diastolic) after the subject sits quietly for at least 5 minutes
- Height (at Visit 1 only)
- Weight (at Visit 1 only).

Any measure that is, in the opinion of the investigator, abnormal AND CR must be recorded as history if found prior to the start of the first study medication application at or as an AE if found after the first study medication application begins.

A systolic blood pressure >140mm Hg or a diastolic blood pressure >100mm Hg is considered abnormal and therefore must be defined as CR or NCR in the CRF.

A weight >300 lbs. is considered abnormal and therefore must be defined as CR or NCR in the CRF.

7.1.7 Urine pregnancy tests

At Visits 1, 2 (prior to randomization), 4, 5, 6, 7, 8 and 9, the investigator or designee will perform a urine pregnancy test for subjects who are WOCBP. The urine pregnancy test kits used must have a minimum sensitivity of 25-mIU ß-HCG/milliliter (mL) of urine.

Subjects who are WOCBP must have a negative pregnancy test result at Visit 1 to be enrolled in the study and at Visit 2 to be randomized.

If the result of any post-treatment urine pregnancy test is positive, the subject will be withdrawn from the study and the subject's pregnancy documented and followed.

7.2 Efficacy Assessments

The following efficacy assessments will be conducted by the appropriate investigational center staff and according to the noted schedules.

7.2.1 Target cNF dimensions

At Visits 1, 2 (prior to the first study medication application), 4, 5, 6, 7, 8 and 9 the investigator will measure the length, width, and height above surrounding skin, in millimeters (mm) of each Target cNF using the ruler provided by NFlection Therapeutics, Inc.

At Visits 1 and 2, to be enrolled in the study a subject's Target cNFs located on the face must each have a length ≥5mm and ≤14mm, a width ≥5mm and ≤14mm and a height ≥2mm. Target cNFs located on the anterior trunk or upper extremities must each have a length of ≥7mm and ≤14mm, a width of ≥5mm and ≤14mm and a height of ≥2mm.

The investigator must report the following dimensions to the nearest 0.5mm using the half-millimeter graduated side of the ruler:

1. Determine if a clinically visible cNF tumor meets the inclusion criteria of the study protocol.

   The identified area of the skin should be examined with a suitable examination light and may be used to determine whether the cNF tumor meets the inclusion criteria. No magnification can be used. Once it has been determined that a qualifying cNF tumor is present, measure the height, length, and width using the procedure described below:

2. Measure the height of the cNF tumor.

   The cNF tumor should be examined with a suitable examination light. Cross lighting (tangential to cNF) may be used. Magnification may NOT be used.

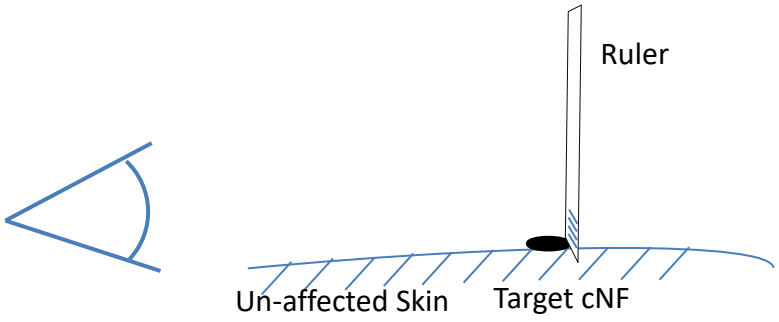
   The height of the cNF tumor should be measured at its highest point above the surrounding non-tumor skin. Use the ruler provided as illustrated below. The ruler should be gently placed on the non-tumor skin directly behind the cNF, perpendicular to the skin without creating a depression on the skin. Examine the visible cNF on a line parallel with the plane of the surrounding non-tumor skin and observe the ruler marking

at the highest point of the lesion. Report the cNF height to the nearest 0.5 mm using the half-millimeter graduated side of the scale.

As a guideline report the cNF tumor height as:

- **0mm:** define 0.5mm as the limit of detectability, therefore any cNF tumor <0.5mm will be rated as 0mm
- **0.5mm:** define 0.5mm as any cNF tumor that is ≥0.5mm and <1.0mm
- **1.0mm:** define 1.0mm as any cNF tumor that is ≥1.0mm and <1.5mm
- **1.5mm:** define 1.5mm as any cNF tumor that is ≥1.5mm and <2.0mm
- **2.0mm:** define 2.0 mm as any cNF tumor that is ≥2.0mm and <2.5mm

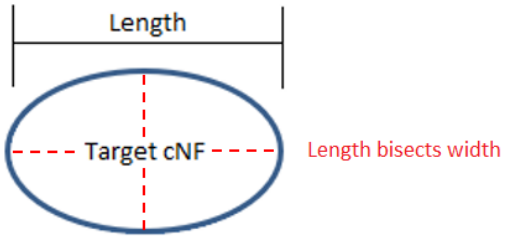
Continue the process described above for cNF tumors with a height greater than 2mm and report the appropriate increment for the cNF height.



3. Measure the length of the cNF.

   The length is the longest measurement from one margin (junction of tumor and non-tumor skin) to the margin directly across an individual cNF tumor. The edge of the ruler denoting 0mm should be placed at the margin of one end and the ruler placed gently on the cNF tumor parallel to the surrounding non-tumor skin. The investigator will then observe the value at the opposite end of the cNF to the nearest 0.5mm. To obtain this measurement the investigator should position their eye directly over the measuring end of the cNF tumor, with the line-of-sight perpendicular to the ruler as it is held parallel to the surrounding non-tumor skin.

   Report the cNF length to the nearest 0.5mm.

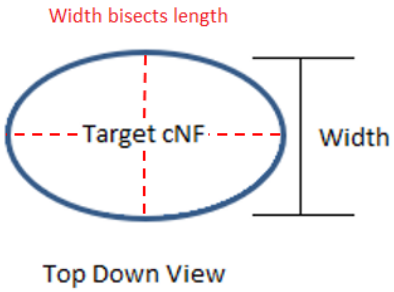


Top Down View

4. Measuring the width of the cNF.

   The width is the measurement of the portion of the cNF tumor that bisects the length perpendicularly. The width should be measured from one margin to the margin directly across the cNF tumor. The edge of the ruler denoting 0mm should be placed at the margin at one end of the width and the ruler placed gently on the tumor parallel to the surrounding non-tumor skin. The investigator will then observe the value at the opposite end of the cNF to the nearest 0.5mm. To obtain this measurement the investigator should position their eye directly over the measuring end of the cNF tumor, with the line-of-sight perpendicular to the ruler as it is held parallel to the surrounding non-tumor skin.

   Report the cNF tumor width to the nearest 0.5mm.



7.2.2 *Physician's Tumor Assessment (PTA)*

The PTA is the investigator's assessment of the average overall severity of each Target cNF at a particular time point. The investigator should NOT refer to any other assessments to assist with these assessments.

At Visits 1, 2 (prior to randomization), 4, 5, 6, 7, 8 and 9, the investigator will conduct the PTA for each Target cNF using the scale below and report the one integer that best describes the average overall severity of each Target cNF. The investigator must complete the PTA after the subject completes the SSA at the visit and prior to the first study medication application at Visit 2.

Physician's Tumor Assessment	
Grade	**Descriptor**
0	Clear/None: no visible cNF (perceptible pigmentary changes may be present)
1	Almost Clear: a slightly visible cNF above the surrounding skin
2	Mild: a noticeably visible/raised dome-shaped cNF
3	Moderate: a moderately raised dome shaped cNF
4	Severe: a significantly raised dome shaped cNF

If during the treatment phase a Target cNF clears (*i.e.*, PTA grade of 0) the subject should continue QD application to the area of the cNF for the remainder of the treatment period.

7.2.3 *Subject's Self-Assessment (SSA)*

The SSA is the subject's assessment of the average overall severity of each Target cNF at a particular time point, it is not a comparison with the SSA at any other time point. The subject should NOT refer to any other evaluation to assist with these assessments.

At Visits 2 (prior to the first study medication application), 4, 5, 6, 7, 8 and 9, each subject will evaluate each Target cNF using the scale below and report the one integer that best describes the average overall severity of the Target cNF. The subject must complete the SSA prior to the PTA at the visit and prior to the first study medication application at Visit 2.

To perform the SSA an investigational center staff member other than the investigator will complete the header on the SSA Scoring Report, provide the report to the subject and identify the first Target cNF to be evaluated. The staff member will identify the Target cNFs by Target cNF ID number, in ascending numerical order starting with the lowest available number. The staff member will then instruct the subject to perform the SSA for the first Target cNF using the scales below. This process of the staff member identifying a Target cNF and the subject performing the SSA will continue until the subject has performed the SSA for each of their Target cNFs. The staff member will collect the SSA Scoring Report and maintain it as a source document.

Subject's Self-Assessment	
Grade	**Descriptor**
0	Clear: no visible cNF
1	Almost Clear: a slightly visible cNF
2	Mild: a noticeably visible/raised cNF higher than the surrounding skin
3	Moderate: a moderately visible/raised cNF higher than the surrounding skin
4	Severe: a prominently visible/raised cNF higher than the surrounding skin

The subject will be allowed to take as much time as needed to complete the SSA.
The staff member must not influence the subject's assessment, explain the grades, or grade descriptors or in any way assist the subject with the SSA evaluations.

Both the subject and the staff member must initial and date the SSA Scoring Report to indicate that the evaluation was completed as instructed. The staff member will collect the SSA Scoring Report and maintain it as a source document.

7.3 Other Assessments

The following assessments will be conducted by the appropriate investigational center staff and according to the noted schedules.

7.3.1 Demographics

At Visit 1, the investigator or designee, will collect demographic information for the subject including date of birth, race, ethnic group, and sex at birth according to local regulations. For countries where local regulatory guidelines prohibit capture of full date of birth, partial date will be recorded in line with local regulations. In addition, medical and surgical history, NF1 history, and concomitant illness(es) will be recorded.

7.3.2 Pharmacokinetic blood samples

For select sites participating in Pharmacokinetic (PK)sampling at Visit 4, blood samples for PK analysis of NFX-179 will be collected by a qualified investigation center staff member. The PK blood draw should not be in the target tumor being treated. Subjects must apply the study medication 4 (±2) hours prior to this visit. The following data will be collected:

- Date and time of last study medication application
- Date and time of pharmacokinetic sampling collection

Refer to the laboratory manual(s) for the collection procedures and the total volume of blood collected.

7.3.3 Patient reported outcome measures (PROM)

The PROM is the subject's assessment of their experience with 9 items for each Target cNF.

Subjects will complete the PROM at Visits 2 (prior to the first study medication application), 6 and 8 using the scales below.

To perform the PROM an investigational center staff member other than the investigator will complete the header on the PROM scoring report, provide the report to the subject, identify the Target cNFs to be assessed by Target cNF ID number, in ascending numerical order starting with the lowest available number and instruct the subject to perform the PROM for the first Target cNF using the scales below. This process of the staff member preparing the PROM Scoring Report, identifying the Target cNF to be assessed and instructing the subject to perform the PROM will continue until the subject has assessed the PROM for each of their Target cNFs.

1. In the past week, **how sensitive (tender) to the touch** was this cNF? □ Not at all □ A little bit □ Moderately □ Quite a bit □ Extremely
2. In the past week, **how severe** was the **pain** you experienced because of this cNF? □ No pain □ Mild □ Moderate □ Severe □ Very severe
3. In the past week, **how severe was the itch** for this cNF? □ No itch □ Mild □ Moderate □ Severe □ Very severe
4. In the past week, how **noticeable** do you think this cNF was? □ Not at all □ A little bit □ Moderately □ Quite a bit □ Extremely
5. In the past week, how would you rate the **size** of this cNF? □ Tiny □ Small □ Medium sized □ Large □ Very large
6. Overall, in the past week, how would you rate the severity of the **appearance** of this cNF? □ Not at all severe □ Mild □ Moderate □ Severe □ Very severe
7. In the past week, **how much** have you had to be **careful to avoid irritating** this cNF? □ Never □ Rarely □ Sometimes □ Often □ All of the time
8. In the past week, **how much** has this cNF **bothered** you? □ Never □ Rarely □ Sometimes □ Often □ All of the time
9. In the past week, **how self-conscious** were you about this cNF? □ Not at all □ A little bit □ Moderately □ Quite a bit □ Extremely

At Visit 8, in addition to the items above each subject will assess their experience since they started using the study medication with global items graded using the following scales:

1. a) Please choose the response below that best describes the **change** in **this cNF overall** since you started using the study medication:

   □ Very much better
   □ Much better
   □ A little better
   □ No change
   □ A little worse
   □ Much worse
   □ Very much worse

   b) Do you consider this change in your cNF overall to be meaningful?
   □ Yes
   □ No

2. a) Please choose the response below that best describes the **change** in the **size** of this cNF since you started using the study medication:

   □ Very much smaller
   □ Much smaller
   □ A little bit smaller
   □ No change
   □ A little bit bigger
   □ Much bigger
   □ Very much bigger

   b) Do you consider this change in the size of your cNF to be meaningful?
   □ Yes
   □ No

The subject will be allowed to take as much time as needed to complete the PROM.
The staff member must not influence the subject's assessment, explain the grades, or grade descriptors or in any way assist the subject with the PROM evaluations.

Both the subject and the staff member must initial and date the PROM Scoring Report to indicate that the evaluation was completed as instructed.

The staff member will collect the PROM Scoring Report and maintain it as a source document.

7.3.4 Standardized Photography

At Visits 1, 2 (prior to the first study medication application), 6, 8 and 9, an appropriately trained investigational center staff member other than the evaluating investigator will take standardized photographs of the subject's Target cNFs.

The Visit 1 and Visit 2 study photographs are to document the location of the cNFs and to assist with locating the cNFs at subsequent visits.

In addition, the Visit 2, 6, 8 and 9 study photographs will be used to calculate the dimensions of the Target cNFs. These measurements will NOT replace the specified Target cNF tumor dimension ruler measurements.

As part of the photography process the investigator that evaluates a subject's Target cNFs at Visits 1, 2, 6, 8 and 9 must outline the perimeter of the Target cNF following the photography system instructions.

For Visits 1, 2, 6 and 8 the investigator must complete this Target cNF outlining process. prior to the subsequent study visit. The investigator may not view the photographs from any other study visit while performing the outlining process or use the study photographs to assist with any evaluations.

Other than performing the required Target cNF outlining process the investigator is not allowed to participate in the photography process or to use the study photographs to assist with any Target cNF evaluations. The only exception to this restriction is noted below.

> **The investigator may view the Visit 2 photographs, and only the Visit 2 photographs, to assist with determining the location of the Target cNFs at Visits 3-9 only if there is no other option to locate the cNFs. If the investigator views the Visit 2 photographs for this purpose the details of the situation must be reported in the subject's study file and on the CRFs.**

The subject's identity will not be revealed in the study photographs.
Equipment, supplies, training, and detailed instructions for obtaining and managing the photographs will be provided to each investigational center prior to the initiation of subject enrollment.

8 ADVERSE EVENTS

All subjects who apply study medication will be assessed for safety.

The investigator is responsible for monitoring the safety of the subjects who are enrolled in this study and for alerting NFlection regarding any event that seems unusual, even if this event may be considered an unanticipated benefit to the subject. The investigator is responsible for appropriate medical care of subjects during the study.

8.1 Definitions

8.1.1 Adverse Event (AE)

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

Thus, any new, CR worsening of an existing sign, symptom, or disease, should be considered an AE.

Worsening of any Target cNF study assessment (*e.g.*, LTA signs and symptoms) should be reported as an AE only if the use of the study medication is interrupted or discontinued or other therapy is required to manage the event.

Every new episode or clinically relevant worsening of a chronic condition (*e.g.*, headaches, allergies, depression, and hypertension) should be reported as a separate AE, even if the condition is reported in the subject's medical history.

The investigator should, when certain, report a diagnosis rather than the signs, symptoms or clinically relevant abnormal laboratory values associated with the AE. Otherwise, signs, symptoms or abnormal laboratory values may be used to describe the AE.

An abnormality (*e.g.*, clinically relevant laboratory abnormalities) discovered prior to the first study medication application, should be reported as medical history, not as an AE.

8.1.2 Serious Adverse Event (SAE)

A Serious Adverse Event is any untoward medical occurrence that at any dose:

- Results in death
- Is life threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity, or
- Is a congenital anomaly/birth defect
- Is an important medical event.

The term "life threatening" refers to an event in which the subject was at risk of death at the time of event; it does not refer to an event that hypothetically might have caused death if it was more severe.

Inpatient hospitalization is considered to have occurred if the subject is admitted to the hospital on an in-patient basis even if released the same day. Prolongation of hospitalization is defined as an additional night stay in the hospital. Hospitalization for a diagnostic test (even if related to an AE) or elective hospitalization that was planned before study enrollment are not themselves reasons for an event to be defined as a SAE.

Important medical events are those that may not be immediately life threatening, result in death, hospitalization but are clearly of major clinical significance and may jeopardize the subject or require intervention to prevent one of the outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalization.

8.1.3 Unexpected Adverse Event

An unexpected AE is any AE that the investigator defines as related to a study medication, the nature of which is not consistent with the Investigator's Brochure or package insert.

8.1.4 Adverse Events of Special Interest

The following are considered AEs of special interest, based on the route of administration, toxicology profile for NFX-179: adverse events related to kidneys, liver, coagulation, and the immune system. Reference is made to the IB for further details.

8.2 Reporting Adverse Events

The investigator is responsible for ensuring that all AEs and SAEs are recorded in the subject's medical record, AE CRF, and SAE form (if applicable), and reported to NFlection. The AE CRF must be used to report both AEs and SAEs. SAEs must also be reported on the appropriate SAE form.

8.2.1 Adverse event reporting period

The investigator must start reporting non-serious AEs and SAEs from the time of the start of the subject's first study medication application until the end of the subject's study participation, or until 30 days after the last study medication application, whichever is longer, whether or not they are considered related to the study.

8.3 Assessment of Adverse Events

The investigator is responsible for assessing the severity, seriousness, and causality of AEs.

8.3.1 Severity of Adverse Events

The investigator is to define the severity of each AE using the following definitions as a guideline. The investigator will consider the range of the possible severity of the event and identify the severity that is the most appropriate according to her/his medical judgment:

- **Mild** – Awareness of signs or symptom, but easily tolerated
- **Moderate** – Discomfort, enough to cause interference with usual activity
- **Severe** – Incapacitating with inability to perform usual activity.

8.3.2 Relationship to Study Medication

The investigator will determine if there is a reasonable causal relationship between the study medication and an AE or not. The investigator will use her/his best medical judgment and consider all relevant factors (*e.g.*, temporal relationship, location of the event, the subject's relevant medical history, concomitant therapies, and concurrent conditions) to determine the relationship of the AE to the study medication.

The investigator will define the relationship of an AE to the study medication by selecting one of the following categories:

- **Related** – There is a reasonable causal relationship between the study medication and the AE
- **Not Related** – There is not a reasonable causal relationship between the study medication and the AE.

The expression "reasonable causal relationship" is meant to convey in general that there are facts (evidence) or arguments to suggest a causal relationship.

8.4 Procedures for reporting non-serious adverse events

At each post-randomization visit, the investigator will question the subject to elicit AEs using a non-directive question such as "Has there been any change in your health since the previous study visit?" If appropriate, based on the subject's response to non-directed questioning to elicit AEs, the investigator will follow-up with directed questions and appropriate evaluations.

Any AE noted during the reporting period must be reported in the source documents and on the appropriate AE CRF. AEs that are defined as "Not Related" to the study medication will be followed until they are resolved or until the subject's last study visit. AEs that are defined as "Related" to the study medication will be followed until they are resolved or, if not resolved after the subject's last study visit, until in the opinion of the investigator, the AE reaches a clinically stable outcome with or without sequelae.

8.5 Procedures for reporting serious adverse events

Medical Monitor
SAE Email: [redacted]
24-hour telephone: [redacted]

Upon becoming aware of a SAE occurring during the AE reporting period, whether or not related to the study medications, the investigator must:

1. Take the appropriate medical action to ensure the subject's safety.
2. Immediately inform the Medical Monitor of the SAE by email (SAE Email address above), ensuring that the subject information is deidentified (only subject initials and subject identifier)
3. Print a copy of the email and place in the study file.
4. Within 24 hours complete, as fully as possible, an AE CRF and an SAE form; e-mail the forms and any other relevant documentation (*e.g.*, concomitant medication CRF, medical history CRF, laboratory test results, etc.) to the Medical Monitor.
5. Monitor and document the progress of the SAE until it resolves or, if not resolved after the subject's last study visit, until in the opinion of the investigator the SAE reaches a clinically stable outcome with or without sequelae AND the investigator and Medical Monitor agree that the SAE is satisfactorily resolved.
6. Inform the Medical Monitor of SAE updates, via telephone, followed by an SAE form update sent by e-mail.
7. Comply with the appropriate regulatory requirements and NFlection instructions regarding reporting of the SAE to the responsible Institutional Review Board (IRB) or Ethics Committee (EC).

The investigator will define the severity of every AE as Mild, Moderate, or Severe using the following intensity grades definitions:

- **Mild** – Awareness of signs or symptom, but easily tolerated
- **Moderate** – Discomfort, enough to cause interference with usual activity
- **Severe** – Incapacitating with inability to perform usual activity.

Note the distinction between an AE with an intensity of "severe" and a "serious" AE, a severe event is not necessarily a serious event. For example, a headache may be severe but would not be classified as serious unless it met one of the SAE criteria.

8.6 Pregnancy

Medical Monitor
SAE Email: [redacted]
24-hour telephone: [redacted]

If a female subject becomes pregnant during the treatment period or within 6 months after the last study medication application, a Pregnancy Report form should be completed. While not an AE or SAE the investigator must submit the completed Pregnancy Report form to the Medical Monitor within 24 hours of learning of the pregnancy.

Abortion, whether therapeutic or spontaneous, will also be reported on a Pregnancy Report form and sent to the Medical Monitor. If the abortion meets seriousness criteria, this information will be captured on the AE CRF and SAE form.

Any congenital anomaly/birth defect in a child born to a female subject should be recorded and reported as an SAE.

8.6.1 Woman of Childbearing Potential (WOCBP)

WOCBP includes any female who has experienced menarche and who has not undergone successful surgical sterilization (*e.g.*, hysterectomy, bilateral tubal ligation, bilateral occlusion of the fallopian tubes or bilateral oophorectomy) or is not postmenopausal. Postmenopausal is defined as ≥12 months with no menses without an alternative medical cause. WOCBP must have a negative UPT at Visit 1 to be enrolled in the study and at Visit 2 to be randomized to study medication.

8.6.2 Protocol approved methods of birth control

The investigator will discuss the potential risk factors associated with pregnancy and the importance of maintaining a highly effective method of birth control with all WOCBP. All WOCBP must use a protocol approved method of birth control throughout the duration of the study and for 30 days after the last study medication application.

For this study protocol approved methods of birth control include:

- Women who are abstinent from reproductive sex as a matter of lifestyle (*i.e.*, women having sex with women); or who are abstinent are acceptable methods of contraception (as these methods, if followed consistently, are at least as effective as hormonal birth control pills)
- Women who are in a monogamous relationship with a partner who has a vasectomy
- Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Transdermal
    - Intravaginal
- Progestogen-only hormonal contraception associated with inhibition of ovulation:
    - Oral
    - Implantable
    - Injectable
- Intrauterine device (IUD)
- Intrauterine hormone-releasing system
- Vaginal gel
- Double-barrier methods (*e.g.*, condoms with spermicide, diaphragm/cervical cap with spermicide).

WOCBP must be on at least 1 protocol approved method of birth control for the following time periods prior to Visit 1:

- Abstinence (≥30 days)
- Partner with vasectomy (≥30 days)
- Vaginal gels (≥30 days)
- Implants (on a stable dose for ≥30 days)
- Injectables (on a stable dose for ≥30 days)
- Patches (on a stable dose for ≥30 days)
- Combined oral contraceptives (on a stable dose for ≥30 days)
- Intrauterine devices (inserted for ≥30 days).

Prior to trial enrollment the investigator must discuss with all WOCBP the potential risk factors associated with a pregnancy during the study and the importance of avoiding pregnancy during study participation. The subject must sign an informed consent form documenting this discussion. During the trial, all WOCBP will be instructed to contact the investigator immediately if they suspect they might be pregnant (*e.g.*, missed or late menstrual period).
If a subject or investigator suspects that the subject may be pregnant prior to study medication administration, the study medication must be withheld until the results of a pregnancy test are

available. If pregnancy is confirmed, the subject must not receive study medication and must be discharged from the study.

If, following the first study medication application it is determined that the subject may have been or was pregnant at the time of study medication exposure (including 30 days after the last study medication application) the investigator must immediately notify the Medical Monitor and record the pregnancy on a pregnancy surveillance form. While not an AE or SAE, the investigator must report every pregnancy using a pregnancy surveillance form and follow the same reporting procedures as described for reporting an SAE.

Protocol-required procedures for trial discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (*e.g.*, x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the investigator must report follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome on the pregnancy surveillance form. Infants should be followed for a minimum of six weeks.

9 STATISTICAL METHODOLOGY

9.1 Sample Size Determination

This is a Phase 2b study designed to evaluate the safety and efficacy of two doses of NFX-179 Gel in comparison to Vehicle Gel. Approximately 168 subjects with cNF are planned to be randomized in the study. The sample size has been chosen to assure at least 150 randomized subjects complete the study. It is based on the assumption that the proportion of responders will be approximately [redacted] in the vehicle treated group and at least [redacted] in the most effective active treated group. Alpha two-tail is 0.05. Under these assumptions power is expected to be at least 90% given the planned sample size.

9.2 Randomization

Subjects will be randomized with a treatment allocation ratio of 1:1:1 (NFX-179 Gel [redacted] to NFX-179 Gel [redacted] to Vehicle Gel).

9.3 Statistical Analyses

9.3.1 General Approach

All randomized and treated subjects will be assessed in analyses of safety and efficacy. Descriptive statistics will be produced on relevant screening and baseline data and on demographic characteristics. Safety and efficacy endpoints will be summarized descriptively by treatment (when applicable) and for all subjects combined and may be analyzed using appropriate parametric or nonparametric inference tests. Comparisons between NFX-179 treated cNFs and vehicle treated cNFs will also performed as described below. Summaries and analyses will be based primarily on non-missing data.

9.3.2 Analysis Populations and Missing-Data Imputation

All subjects who are randomized and dispensed study drug and have at least one post-baseline visit with efficacy evaluations will be included in the intent-to-treat (ITT) population. Missing data imputation procedures based on the ITT population are described below. The Observed Cases (OC) population will include all subjects in the ITT population with observed efficacy data at Visit 8. No data imputation will be used with this population for subjects with missing data at any post-baseline visit.

The Observed Cases (OC) population will be used for primary and secondary efficacy analyses to address the main efficacy evaluation objective of the study. There will also be two sensitivity analyses of efficacy. For the first sensitivity analyses, the Per-Protocol (PP) population, drawn from the OC population subjects who completed the study through Visit 8 with no major protocol violations, will be used. For the second sensitivity analyses, the ITT population will be used, and all missing post-baseline efficacy data will be imputed using last observation carried forward (LOCF) from the last available observed efficacy data after the Baseline visit. Mixed Model-based missing data imputation or Multiple Imputation may be used as a supplementary imputation method. A supplemental efficacy analysis based specifically on subject Responders will also be conducted using the ITT population where subjects terminating the study before completing Visit 8 due to treatment-related adverse events will be imputed as Non-Responders. All efficacy analyses will perform separate

comparisons of each Active treatment group with the Vehicle group along with other contrasts described below. No adjustments for multiplicity will be made. All subjects who are randomized, received at least one confirmed dose of study drug, and have at least one post-baseline safety evaluation will be included in the Safety Population.

9.3.3 Safety

Safety Endpoints:

- Adverse events
- Local tolerability including:
    - erythema
    - edema
    - scabbing/crusting
    - vesiculation
    - erosion
    - stinging
    - burning
    - pruritis
- Clinical laboratory assessments.

9.3.4 Baseline Assessment

Descriptive statistics will be performed on relevant Visit 1 and Visit 2 data (*i.e.*, data collected prior to the treatment administration) and on demographic and baseline disease severity characteristics. There will be no statistical hypothesis testing of baseline data.

9.3.5 Efficacy Analyses

9.3.5.1 Overview

Analyses of efficacy parameters collected at the tumor level will primarily be performed at the tumor level, under the assumption that tumor responses within the same subject will be predominantly statistically independent. Those parameters include results based on tumor dimensions, SSA and PTA evaluations, and responder analyses based on any of these measures. This approach is consistent with the topical application of the study medication to individual tumors and the assumption of minimal systemic absorption or systemic action of the study medication. The statistical assumption of within-subject tumor response independence will be evaluated using the appropriate Shrout-Fleiss intraclass correlation based on tumor changes from

baseline. For this study, that statistic is assumed to be less than 0.25. If this assumption is confirmed, analyses conducted at the subject level will then be performed as supplementary analyses. Tumor volume is the primary measurement of interest; however, the ruler measurements of tumor area, length, width and height will also be analyzed as supplementary analyses, using the analysis models applied to tumor volume.

If the Shrout-Fleiss intraclass correlation statistic is equal to or greater than 0.25, then subject-level efficacy parameter analyses will be considered primary, and tumor-level efficacy parameter analyses will be considered supplementary. In either case, results from both types of analyses will be presented.

9.3.5.2 Contrasts

In order to fully understand the dose response results and achieve greater sensitivity to detect effectiveness for the active treatments, comparisons among the three treatment groups will include the following: pairwise contrasts between each active treatment group vs vehicle; a contrast between the [redacted] treatment group and the [redacted] treatment group; and a contrast between the average of the [redacted] and [redacted] treatment groups vs vehicle. In addition, all analyses and contrasts will be conducted separately for each lesion body location: Face, anterior trunk, and upper extremities.

9.3.5.3 Endpoints

The safety endpoint is to determine the safety of treatment with NFX-179 Gel ([redacted] and [redacted] or Vehicle Gel applied QD for 182 days of treatment. The results of dermal safety and local tolerability assessments including pain/burning, itching, erythema, edema, scabbing/crusting, and vesiculation/erosion will be summarized by treatment group and visit. The evaluation of adverse events will be based on summaries and listings of adverse events by treatment group, as described below under Safety Analyses. If tumor independence is confirmed as discussed above, the primary efficacy endpoint will be a dichotomized analysis conducted on the proportion of tumors achieving a reduction from baseline volume of at least 50%. A Chi-square analysis at the tumor level will be performed as the primary analysis between vehicle and each active treatment group. Otherwise, if tumor independence is not confirmed, the primary efficacy endpoint will be analyzed at the subject level. The primary efficacy analysis will then be a dichotomized Chi-square Responder analysis at the subject level. It will be based on the proportion of subjects considered to be Responders, where a Responder is defined as a subject

for whom at least 5 treated tumors showing the greatest tumor-level percent reduction from baseline volume have a percent reduction from baseline of at least 50%.A Chi-square analysis with contrasts as outlined above will be used. At the subject-level analysis, an Analysis of Variance will also be used to analyze the per-subject mean percent of tumor responders, with contrasts as described above. Treatment groups may also be compared using appropriate mixed-model logistic regression incorporating both tumor- and subject-level information. Supplementary analysis similar to those described above will also be conducted based on threshold reductions from baseline volume of at least 25%, 30%, 60% and 75%.The first secondary efficacy endpoint is to determine the clinical efficacy of NFX-179 Gel defined as the mean percent change in neurofibroma volume after 182 days of treatment based on tumor volume derived from ruler measurements. Analyses of Variance will be conducted both on the tumor level and the subject level, including the contrasts as described above. The determination of whether the tumor-level or subject-level analysis will be considered preferentially will be based on the outcome of the tumor independence assessment described above. The non-primary analysis will be considered as a supplementary analysis.Additional secondary efficacy endpoints include the analysis of change from baseline in the Physician's Tumor Assessment grade and the Subject's Self-Assessment grade after 182 days of treatment. These will be analyzed analogously to the primary endpoint using an Analysis of Variance and contrasts described above. In addition, for each assessment dichotomized analyses will be conducted on the proportion of tumors achieving a grade of Clear, the proportion of tumors achieving a grade of either Clear or Almost Clear, the proportion of tumors achieving at least a grade 1 improvement, and also a 2 grade or greater improvement from baseline after 182 days of treatment. Treatment groups will be compared using separate Chi-square analyses. An appropriate mixed-model logistic regression may also be used, as well as an ANOVA analysis of within-subject averaged results across tumors. Contrasts as described above will be used.

Analyses similar to those described above will be conducted based on tumor area and tumor length.

Efficacy analyses at post-baseline visits prior to Day 182 where efficacy data are collected will also be performed using the models described above. These will be considered exploratory in nature.

Analyses will also be performed to examine the strength of relationship between tumor volume Responders (as defined above), and PROM Responders defined as subjects indicating improvement based on Visit 8 Supplementary PROM items and also indicating the improvement was meaningful. These analyses will include appropriate correlation evaluations for dichotomous parameters, as well as odds-ratio analyses and related 95% confidence limits. These analyses will be conducted at both tumor and subject levels.

The psychometric properties of the PRO measure will be analyzed under a separate statistical analysis plan.

9.3.6 Safety Analyses

Subjects will be assessed for the occurrence of new and ongoing AEs. Descriptions of AEs will include the dates of onset and resolution (if resolved), maximum severity, seriousness, and action taken regarding the study drug, corrective treatment, outcome, and investigator's assessment of causality. All AEs will be recorded and classified using terminology from the Medical Dictionary for Regulatory Activities (MedDRA). All reported treatment-emergent AEs (TEAEs), defined as any AE with an onset on or after the date of first study drug application, will be summarized by treatment group, the number of subjects reporting TEAEs, system organ class, preferred term, severity, and relationship to study drug. When summarizing TEAEs by severity or relationship to study drug, each subject will be counted only once within a system organ class or a preferred term using the event with the greatest severity or causality, respectively, within each category. All reported SAEs will be summarized by treatment group, the number of subjects reporting SAEs, system organ class, preferred term, severity, and relationship to study drug.

All information pertaining to AEs noted during the study will be listed by subject and will include a verbatim description of the event as reported by the investigator, as well as the preferred term, system organ class, start date, stop date (if stopped), seriousness, severity, action taken regarding the study drug, corrective treatment, outcome, and relationship to the study drug. In addition, a listing of subjects who prematurely discontinue from the study due to AEs will be provided as well as a listing of subjects who reported an SAE.

Changes from baseline in safety laboratory values, local tolerability assessments, and vital sign measurements will be summarized with descriptive statistics for each treatment group at

all applicable study visits.

Shift tables will be presented for changes in safety laboratory values to summarize laboratory test results collected at all visits. Normal ranges established by the central laboratory will be used to determine the shifts. A listing of all out-of-range laboratory test results at any assessment time point will also be provided. Determination of clinical significance for all out-of-range laboratory values will be made by each investigator and included in the listing. In addition, a listing of all clinically significant laboratory test results will be provided.

Other safety assessments, including vital signs, physical examination data and LTA data will be summarized by treatment group.

9.4 Missing Data

Unless otherwise specified, summaries and analyses will be based on non-missing data, with the number of non-missing observations included in the summary. The use of methods to impute missing data. including LOCF, is discussed above.

9.5 Sub-Group Analyses

Exploratory efficacy investigations may be carried out based on subject gender, subject age, time since onset of NF1 diagnosis and/or cNF appearance, cNF classification, baseline tumor size, study medication compliance, and other factors.

Exploratory safety investigations may be carried out based on subject gender and age.

Exploratory sub-group analyses of safety parameters may be conducted based on time since CNF diagnosis, age at onset, study medication use per day, and other parameters.

10 TRAINING, DATA HANDLING AND RECORD KEEPING

10.1 Training

For each investigational center, the study staff, including the investigator and subinvestigator(s) will be trained to the protocol, study specific procedures, and the paper CRFs or eCRFs (CRFs). Those unable to attend the training must receive on-site training from an appropriately trained individual prior to participating in any of the procedures and evaluations in this study.

Clinical Research Associates (CRAs) and other applicable personnel will be trained prior to study initiation to familiarize CRAs with the disease, the Standard Operating Procedures (SOPs),

the protocol and other study specific items. Team organization, communication and operational issues will also be discussed.

NFlection or designee will provide an investigational center file to each center.

10.2 Data Collection

The investigator must maintain required records for all study subjects. Data for this study will be recorded in the subject's source document and on the CRFs. All data on these CRFs should be recorded completely and promptly. A copy of the completed CRFs for each subject will be retained by the investigational center.

Records of the subject's participation in this study will be held confidential except as disclosure is required by law. The investigator, NFlection, persons working on behalf of NFlection, and under certain circumstances, the United States Food and Drug Administration and the Institutional Review Board will be able to inspect and copy confidential study-related records that identify subjects by name. Therefore, absolute subject confidentiality cannot be guaranteed. If the results of this study are published or presented at meetings, the subject's identity will not be revealed.

10.3 Data Management

Data Management activities of this study will be subcontracted. Edit checks and review processes will be performed by the sub-contractor until all data clarifications are resolved. The data will be exported to be stored in SAS datasets (or equivalent) by the sub-contractor. After all data clarifications are resolved and subject's evaluability is determined, the database will be locked.

10.4 Study Monitoring

Before an investigational center can enter a patient into the study, a representative of NFlection or its designee, will visit the investigational study site to:

- Determine the adequacy of the facilities
- Discuss with the investigator(s) and other personnel their responsibilities regarding protocol adherence, and the responsibilities of NFlection or its representatives. This will be documented in a Clinical Study Agreement between NFlection and the investigator.

During the study, a study monitor from NFlection or its designee, will have regular contacts with the investigational center, for the following:

- Provide information and support to the investigator(s)
- Confirm that facilities remain acceptable
- Confirm that the investigational center staff is adhering to the protocol, that data are being accurately recorded in the CRFs, and that study medication accountability checks are being performed
- Perform source data verification. This includes a comparison of the data in the CRFs with the subject's study records at the investigational center, and other records relevant to the study. This may require direct access to all original records for each subject (*e.g.*, clinic charts).
- Record and report any protocol excursions not previously sent to NFlection
- Confirm non-serious AEs and SAEs have been properly documented on CRFs and confirm any SAEs have been forwarded to NFlection and those SAEs that met criteria for reporting have been forwarded to the IRB.

The study monitor will be available between visits if the investigator(s) or other investigational center staff needs information or advice.

10.5 Source Documentation

Investigators must keep accurate separate records (other than the CRFs) of all subjects' visits that include all pertinent study related information. A statement should be made indicating that the subjects have been enrolled in this clinical study and have provided written informed consent. Any AEs must be completely documented. Source documentation includes results of any diagnostic tests conducted during the study.

10.6 Inspection of Records

A NFlection individual or designee will be allowed to conduct site visits to the investigational center facilities for the purpose of monitoring any aspect of the study. The investigator agrees to allow the study monitor to inspect the drug storage area, study medication stocks, drug accountability records, subject charts and study source documents, and other records relative to study conduct.

10.7 Retention of Records

The investigator must maintain all documentation relating to the study for a period of 2 years after the last marketing application approval, or if not approved 2 years following the discontinuance of the study medication for investigation. If it becomes necessary for NFlection or the Regulatory Authority to review any documentation relating to the study, the investigator must permit access to such records.

11 QUALITY CONTROL AND QUALITY ASSURANCE

The study is conducted under the sponsorship of NFlection in compliance with the applicable regulatory requirements as well as applicable ICH guidelines, Declaration of Helsinki, and in respect of the sponsor and/or sub-contractor SOPs for study conduct and study monitoring.

Audits may be carried out by NFlection or designee, and inspections may be performed by regulatory authorities or IRB/ECs before, during or after the study. The investigator will provide the auditing/inspecting group direct access to all study records (*e.g.*, CRFs, subject medical records, study medication dispensing records) and the investigational center study facilities. The investigator and investigational center staff will be available and will assist the auditing/inspecting groups as appropriate.

12 ETHICS

12.1 Ethics Review

This protocol, informed consent form, any information provided to subjects, subject-recruiting advertisements, and any amendments to these items will receive IRB/EC approval prior to use. The IRB/EC must receive a copy of the Investigator's Brochure, all protocol amendments, safety reports and other study related information as required by regulation or the IRB/EC procedures.

12.2 Ethical Conduct of the Study

The rights, safety and well-being of the subjects are the most important considerations in this study and take priority over the interests of society and science.

This study will be conducted in accordance with the ethical principles originating from the Declaration of Helsinki, the current ICH E6 GCP guideline, local regulatory requirements and, at

US investigational centers, in compliance with the HIPAA. The study will be conducted in compliance with the IRB/EC approved version of the protocol and any applicable amendments.

12.3 Written Informed Consent

The investigator(s) at each center will ensure that the subject is given full and adequate oral and written information about the nature, purpose, possible risks, and potential benefits of the study. Subjects must also be notified that they are free to discontinue from the study at any time. The subject should be given the opportunity to ask questions and allowed time to consider the information provided.

The subject's signed and dated informed consent must be obtained before conducting any study procedures. The investigator(s) must maintain the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject.

12.4 Study Conduct and Protocol Amendments

With the exception of eliminating an immediate hazard to a subject, the investigator should not deviate from the protocol or implement any changes without prior written approval from the sponsor representative or designee and prior review and documented approval from the IRB/EC.

Changes that involve only logistical or administrative changes are allowed. The investigator should document and explain any excursion from the protocol. A protocol deviation is a non-adherence to protocol-specific study procedures or schedules that does not increase the risk to a study subject and does not affect the scientific integrity of the study. A protocol violation is any divergence from the protocol-specific study procedures or schedules that may results in an increased risk to a study subject or that affect the scientific integrity of the study. All protocol violations must be reviewed by the Medical Monitor and reported to the IRB by the investigator, as directed by the IRB-specific procedures.

12.5 Regulatory Documents

The investigator must maintain a study file containing current and complete regulatory documentation in compliance with the current ICH E6 GCP guideline. This file will be reviewed

as part of the routine monitoring for this study.

12.6 Contractual Requirements

A contractual agreement will be signed between NFlection and each investigator. This document will contain supplemental information, including financial terms, confidentiality, study schedule, third party responsibility, and publication rights.