CLINICAL STUDY PROTOCOL AMENDMENT

A Randomized, Double-Blind, Vehicle-Controlled, Parallel Group Phase 2a Study to Determine Safety, Tolerability, Pharmacokinetics, and Pharmacodynamic Activity of NFX-179 Gel in Subjects with Cutaneous Neurofibromas

Protocol No.	NFX-179-NF1-201
Protocol/Amendment Date:	20-JUL-2020
Amendment No.:	1
Supersedes:	N/A
Sponsor:	NFlection Therapeutics 714 Woodcrest Road, Wayne, PA 19087 United States
Medical Monitor:	Guy Webster, M.D. Ph.D. 24-hour telephone: (302) 559-8684 Email: GWebster@Nflectionrx.com

PROTOCOL AMENDMENT INVESTIGATOR SIGNATURE PAGE

Protocol Number: NFX-179-NF1-201
Amendment Number: 1

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 AMENDMENT APPROVAL PAGE

Protocol Number: NFX-179-NF1-201
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C. Cole 07-23-2020

Christopher Powala
Chief Executive Officer
NFlection Therapeutics

Date

7/23/2020

Guy Webster, M.D., Ph.D.
Chief Medical Officer
NFlection Therapeutics

Date

TABLE OF CONTENTS

1 AMENDMENT HISTORY

Protocol footer date: 25-MAY-2020
Previous amendments: None

2 AMENDMENT SUMMARY

The following sections of the NFX-179-NF1-201 protocol with footer date 15-MAY-2020 and with a final NFlection Therapeutics approval signature date of 27-MAY-2020 are amended:

- PROTOCOL APPROVAL PAGE (page 3 of 77)
- Section 4.8 Subject discontinuation from the study
- Section 5.2.3 Visits 3 and 4/Days 8 and 15 (QD treatment)
- Section 5.3 Study cNF tumor identification
- Section 6.2.2 Target cNF ultrasounds
- Section 6.3.1 Demographics.

3 AMENDMENT RATIONALE

These protocol changes are made to:

- Correct a typographic error to the protocol number on the PROTOCOL APPROAL PAGE
- Respond to recommendations from the Food and Drug Administration; changes to section 4.8
- Correct an error which instructs the investigator to take standardized photographs at Visits 3 and 4; changes to protocol section 5.2.3
- Add the requirement that for each subject Target cNF Tumor number 5 be on the face; changes to protocol section 5.3
- Update the description of the high frequency ultrasound equipment that may be used; changes to section 6.2.2
- Correct a typographic error; changes to section 6.3.1.

4 PROTOCOL CHANGES

PROTOCOL APPROVAL PAGE (page 3 of 77):

Previous protocol number:
NFX-179-NF-201.

Changed protocol number:
NFX-179-NF1-201.

Section 4.8 Subject discontinuation from the study:

Previous paragraph 2:
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. 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 NFlection study monitor.

Changed paragraph 2:
The investigator will 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 NFlection study monitor.

Section 5.2.3 Visits 3 and 4/Days 8 and 15 (QD treatment):

Previous procedure 7:
Take standardized color photographs of each Target cNF Tumor.

Changed procedure 7:
Procedure 7 is deleted.

Section 5.3 Study cNF tumor identification:
Previous paragraph 3 major bullet 3:

- 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 and areas within 5mm of the orbital rim.

Changed paragraph 3 major bullet 3:

- Face (Target cNF Tumor #5 must be on the 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 and areas within 5mm of the orbital rim.

Previous paragraph 5 bullet 5:

- Target cNF Tumor #5/green ID stickers

Changed paragraph 5 bullet 5:

- Target cNF Tumor #5/green ID stickers (Target cNF Tumor #5 must be on the face).

Section 6.2.2 Target cNF ultrasounds:
Previous paragraph 2:
The HFUS results will be used to determine the volume of the Target cNF. HFUS imaging will be performed using the Vevo3100-System.

Changed paragraph 2:
The HFUS results will be used to determine the volume of the Target cNF. HFUS imaging will be performed using an appropriate HFUS system (*e.g.*, Vevo3100, GE Logiq E, etc.).

Section 6.3.1 Demographics:
Previous paragraph 1 sentence 3:
In addition, medical and surgical history, EN history, and concomitant illness(es) will be recorded.

Changed paragraph 1 sentence 3:
In addition, medical and surgical history, NF1 history, and concomitant illness(es) will be recorded.