Clinical study protocol

Project Name: A prospective, single-arm, phase II clinical study of selmetinib hydrosulphate capsules for treating postoperative patients with neurofibromatosis type I

Sponsor: Sun Yat-sen Memorial Hospital of Sun Yat-sen University

Version number: V2.0

Version date: 2024.04.17

Project leader: Huang Zhiquan

Scheme signature confirmation:

Compliance Statement

In accordance with the provisions of the Good Clinical Practice for Drug Clinical Trials and the Administrative Measures for Clinical Studies initiated by Medical Institutions (Trial) and the Declaration of Helsinki, we promise to carry out this study according to this protocol. The participants must be trained to conduct the study after the written approval of the Ethics Committee and the written informed consent of the subjects, and the protocol revision shall be re-approved again.

1.Protocol abstract (title, brief description of study, study object, outcome measures, study intervention*, Sample size, etc., in 300-500 words)

This study focuses on patients with neurofibromatosis type I, who lack effective medical therapy and has a high recurrence rate after surgical resection. For patients with small solid tumors, limited space occupying, and not invading the brain, spine and other important organs, surgical treatment is the main treatment means. As a MEK inhibitor, by selectively binding the mitogen-activated protein kinase (MEK) 1 / 2 protein, it can block the mitogen-activated protein kinase / extracellular signal-regulated kinase signaling pathway that regulates key cellular responses, and can induce tumor shrinkage and reduce postoperative recurrence. The purpose of this study is to treat hydrosulphate for patients with surgical indications, to observe the efficacy of drug treatment, consolidate the postoperative efficacy and reduce the recurrence rate. In this study, progression-free survival (PFS) after drug treatment was used as the main study outcome measure, duration of remission (DOR) and objective response rate (ORR) as secondary outcome measures to explore the use of selmetinib sulphate for tumor control efficacy, reduction of recurrence rate, and stability of efficacy in patients with neurofibromatosis type I.

2. Introduction (references to be noted in the introduction)

2.1 Research theoretical basis / background (explain why clinical studies are conducted from the limitations of disease, standard of treatment and known treatment, and explain the findings and importance of preclinical, pharmacological and related studies)

Neurofibromatosis (NF) has been included in the list of rare diseases in many countries including China, 96% of which are NF 1 subtypes, and

the clinical manifestations of NF 1 are diverse[1], Involmultiple systems and can cause serious complications such as airway obstruction, spinal cord compression and motor dysfunction[2-4]. Pleexiform neurofibromas (PN) occur in 30 to 50% of NF 1 patients[5、6], PN progress fast, accompanied by serious appearance defects, high disability, and the risk of deterioration[7-10]. According to the 2023 edition of the multidisciplinary diagnosis and treatment of type I neurofibromatosis, patients with NF 1 are more likely to have a variety of benign and malignant tumors than the normal population, including pNF, CNF, MPNST and OPG. Attention should be paid to the early identification and monitoring of the above tumors. Neurofibromas with accelerated growth, pain and hard texture. At the same time, systemic evaluation should be carried out, and patients with no signs of distant metastasis should undergo early surgical treatment as far as possible, and patients with distant metastasis can choose radiotherapy, chemotherapy and targeted therapy.

Neurofibromatosis type I (neurofibromatosis type 1, NF 1) is an autosomal dominant disorder with 50% of patients with familial and 50% sporadic mutations. NF 1 gene encodes neurofibromin, downregulates the activity of Ras-Raf pathway and suppresses cell proliferation; deficiency in neurofibrosis causes excessive activation of RAS pathway and causes uncontrolled cell proliferation in NF 1 patients[5]. At present stage, surgery is the most commonly used, the main treatment, and neurofibroma has the characteristics of the nerve root growth, it is difficult to solve all lesions through surgery, lesions composed of extensive nerve and vascular tissue and normal tissue, surgical resection difficult and bleeding, incomplete resection after recurrence as high as 50%. NF 1 occurs in the head and neck. Some patients need secondary surgery 1 year after surgery, and the proportion of patients with partial resection after secondary surgery is higher than that of patients with subtotal resection.

Five years after surgery, the proportion of secondary surgery was more than 50%[7]。

As a MEK inhibitor, it blocks the mitogen-activated protein kinase / extracellular signal-regulated kinase signaling pathway by selectively binding to the mitogen-activated protein kinase (MEK) 1 / 2 proteins that regulate key cellular responses[11-13], And then induce tumor shrinkage, creating conditions for disease control, surgical resection, reducing postoperative recurrence and reducing complications. Based on the targeted treatment of hydrogen sulphate smetinib capsule, this study for NF 1 patients, evaluated after enrollment, after the patients with tumor monitoring solid tumor shrinkage effect and the duration of efficacy, and postoperative recurrence time, and then verify the effectiveness of hydrosulphate smetinib capsule to reduce the recurrence rate of NF 1 patients.

2.2 Risk / benefit evaluation

2.2.1 Known potential risks

The potential risks of this study are mainly the adverse reactions after the use of selmetinib hydrosulphate capsules, the hyperprogression of tumor treatment caused by the study protocol itself, and the risk of sudden accidents in the study.

2.2.2 Known potential benefits

The potential benefit of the subjects in this study enables the subjects to achieve partial tumor remission, delay progression, reduce recurrence, and improve function; entering the clinical study can gain more attention from the investigators and handle the disease changes in time, which is beneficial to the treatment of the disease.

2.2.3 Potential risk and benefit evaluation

Smetinib Insulphate capsule is indicated for pediatric patients with

neurofibromatosis type I (NF 1) aged 3 years and older with symptomatic, inoperable plexiform neurofibromas (PN). It was approved to list in China on April 28,2023, and was included in the medical insurance directory on December 13,2023. Several guidelines, consensus and diagnosis and treatment norms in China recommend selmetinib hydrohydrogen sulfate for the treatment of NF 1-PN. The most common toxicity of selmetinib hydrosulphate capsules is grade 1 and 2 gastrointestinal symptoms (nausea, vomiting, or diarrhea), asymptomatic elevated creatine phosphokinase levels, acne-like rash, and paronychia with good safety and tolerability. Therefore, this clinical study protocol has a low risk of disease progression and serious adverse events on the treatment of NF 1[14、15]. At the same time, in the future studies, the investigators will pay more attention to the subjects' systemic condition and tumor treatment condition, and the subjects will also gain some clinical benefit in this study.

3. Study objective and endpoint (list presentation objective (specific issues to be addressed), corresponding to the outcome measures)

3.1 Purpose

3.1.1 Main Purpose

The primary objective of this study is to explore the progression-free survival (PFS) after 6 cycles of selmetinib hydrosulphate capsules in patients with neurofibromatosis type I (NF 1).

3.1.2 Secondary Purpose

The secondary objective of this study is to explore the duration of remission (DOR) and objective response rate (ORR) in postoperative patients with neurofibromatosis type I (NF 1).

3.1.3 Exploratory Purpose

The exploratory purpose of this study is to explore the long-term

efficacy and stability of patients with neurofibromatosis type I (NF 1) treated with selmeetinib capsules.

3.2.study indicators

3.2.1 Main Indicators and Definitions

2-year progression-free survival rate (2-year PFS rate): the rate of no tumor progression or death from any cause within 2 years from postoperative treatment (whichever comes first).

3.2.2 Secondary indicators and Definitions

Duration of response (DOR): the time between the start of CR or PR and the first assessment of PD or death from any cause.

Objective response rate (ORR): the proportion of patients with a 20% tumor reduction for a certain period of time, including complete response (CR) and partial response (PR). The ORR was defined as the proportion of patients with a 20% tumor size reduction in the shortest time period.

3.2.3.safety indicators

The subject's vital signs, blood routine, liver function, blood biochemistry, urine routine, stool routine, coagulation function, left ventricular ejection fraction (LVEF), creatine phosphokinase, vitamin E, and bleeding risk.

4. study population

4.1 Inclusion criteria

(1) Age≥18 years old

(2) According to the updated NF 1 diagnostic criteria of the National Institutes of Health (NIH) in 2021,

① 6 or more CALMs:d> 5 mm before puberty or d> 15 mm after puberty;

② 2 or more neurofibromas of any type or 1 plexiform neurofibroma;

③ Plaques in the axillary or inguinal area;

④ Optic glioma (OPG);

⑤ Slit lamp examination of two or more Lisch nodules, or optical coherence tomography (OCT) / imaging of two or more near infrared (NIR) choroid abnormalities;

⑥ Characteristic bone lesions, such as sphenoid dysplasia and anterolateral curvature of the tibia;

⑦ Pathogenic heterozygous NF 1 variants with allelic variant scores of 50% in normal tissues (such as leukocytes);

Patients with no parental history and fulfilling 2 or more clinical characteristics could be diagnosed with NF 1

Parents with a history of 1 or more clinical features can be diagnosed with NF 1

(3) Before enrollment, a head and neck surgeon performed a pathological biopsy of the solid tumor to clarify the pathological diagnosis and exclude the malignant peripheral schwannoma (MPNST)

(4) At least one measurable tumor lesion according to the efficacy evaluation criteria of solid tumors RECIST 1.1

(5) The tumor did not invade the brain, spine and other important organs, and there are indications for surgical resection and surgical treatment

(6) The performance status of the Eastern Cooperative Oncology Group (Eastern Cooperative Oncology Group, ECOG) was 0-1

(7) Blood routine: white blood cell count (WBC) $3.0 10^9$/ L; Absolute neutrophil count (ANC) $1.5 10^9$/ L; Platelet (PLT) $100 10^9$/ L; hemoglobin level (HGB) 9.0 g/dL (no corresponding supportive care, such as transfusion and increased leukocytes within 7 days).

(8) Liver function: 2.5 times aspartate aminotransferase (AST) and alanine aminotransferase (ALT); albumin (ALB) 30 g / L.

(9) Renal function: serum creatinine 1.5 times ULN or creatinine clearance (CrCl) 50 mL/min (using the Cockroft / Galt formula); urinary protein (UPRO) <(+ +), or 24-hour urinary protein <1.0 g.

(10) Cardiac function: blood creatine phosphokinase 200U / L, left ventricular ejection fraction (LVEF) 50%;

(11) Did not participate in other clinical trials within the previous 30 days;

(12) Patients who voluntarily participate in the project and sign the informed consent form.

4.2 Exclusion criteria

(1) The patient had abnormal blood indexes, abnormal liver and kidney heart function, and cannot tolerate the clinical study process after multidisciplinary consultation and evaluation

(2) The patient has become malignant peripheral nerve schwannoma (MPNST) or has serious complications such as other malignant tumors and heart disease, or has been treated with anti-tumor therapy such as chemotherapy and radiotherapy

(3) The whole clinical study cannot be completed due to personal, social and economic reasons

(4) There are previously serious systemic system diseases and the disease cannot be cured or drug control

(5) Patients who are present in pregnancy

4.3 Lifestyle considerations (lifestyle related restrictions: smoking, drinking, exercise, diet, etc., and what measures will be taken if the subject needs drugs, treatments or surgery prohibited in the protocol)

After entering the clinical study, the subject needs a light diet, food, tobacco, alcohol, and no strenuous exercise. If the subject needs

the drug, treatment or surgery unrelated to the study, the investigator needs to evaluate whether the cause of the need for the drug, treatment and surgical treatment is the adverse event of the study, additional treatment due to accident or other reasons, consider the impact of the treatment on the course of the study, then advise the subject to receive conventional treatment after withdrawal and seal the subject data.

4.4 Screening failures (definition of screening failures and how to process screening failed subjects)

Screening failure refers to the recruitment of subjects who failed to meet the inclusion criteria or the exclusion criteria after multidisciplinary evaluation. The study will inform the results of the multidisciplinary consultation and give the current best treatment advice.

4.5 Recruitment and retention strategy (how to recruit subjects (location, method, expected number.....); How to retain subjects (multiple contact information, incentive); such as involving vulnerable groups: reason + safeguard measures; if having compensation or incentive measures: object, quantity, form, time, etc.)

This study will take offline, combining online recruiting subjects, offline main location for sun Yat-sen memorial hospital oral and maxillofacial surgery, including but not limited to posters, leaflets, lectures and other forms to attract more subjects, each interested patients on-site registration, leave contact information and continue to one-on-one explanation. If the subject is in financial difficulties, the investigator team will assist the subject in providing assistance with the charity fund application to reduce the financial burden of the subject.

5. research design

5.1 Overall design (including assumptions, type, etc.)

This study hypothesized that selmetinib hydrosulphate capsules are effective in neurofibromatosis type I, including improving efficacy after tumor resection, delaying progression, reducing recurrence, and improving function. The prospective, single-arm, phase-study study protocol was designed to estimated progression-free survival (PFS) in more than 50% of NF 1 patients at 24 months, objective response rate (ORR) of 40%, and duration of tumor response (DOR) of 12 months.

5.2 Study design process

5.2.1 Study the specific implementation process

This study started from the recruitment of subjects, with clinical diagnosis, definite diagnosis by pathological biopsy, primary screening according to inclusion criteria and exclusion criteria, and signed informed consent before enrollment. After evaluation as indication for surgical resection and surgical treatment, selmetinib hydrosulphate capsules. PFS, ORR and DOR were assessed after 6 cycles of oral selhydrosulphate capsules (20-50mg bid).

Interview	Screening period	Drug 6 cycles						Follow-up visit			
	V1	V2	V3	V4	V5	V 6	V 7	V 8	V9	V 10	V11
Follow-up time	*1 Day before enrollment*	*And 1 cycle after V 1*	*And 1 cycle after V 2*	*And 1 cycle after V 3*	*Cycle 1 after V4*	*And 1 cycle after V 5*	*And 1 cycle after V 6*	*For 3 cycles after V 7*	*For 3 cycles after V 8*	*And 6 cycles after V 9*	*And 6 cycles after V 10*
Signed the informed consent form	√										
Inclusion / exclusion criteria	√										

Demographic data	√										
medical history	√				√			√	√	√	√
ECOG grade	√	√	√	√	√	√	√	√	√	√	√
check-up	√	√	√	√	√	√	√	√	√	√	√
vital sign	√	√	√	√	√	√	√	√	√	√	√
electrocardiogram	√				√			√	√	√	√
routine blood test	√		√	√	√	√	√	√	√	√	√
Blood biochemical	√		√	√	√	√	√	√	√	√	√
Liver, kidney, and cardiac function	√		√	√	√	√	√	√	√	√	√
coagulation function	√		√	√	√	√	√	√	√	√	√
Heart ultrasound	√				√			√	√	√	√
Pathological biopsy	√										
Infectious disease examination (hepatitis B, hepatitis C, HIV, syphilis)	√										
Imaging examination	√				√			√	√	√	√
complication And adverse event assessment			√	√	√	√	√	√	√	√	√

5.3 Methods to reduce bias (e. g., randomization, blindness, matching method, etc.)

The end of this study was defined as the last subject who completed the last follow-up or was lost to follow-up or died

5.4 Definition of end of study (e. g. last subject completes last follow-up)

5.5 Statistical analysis

5.5.1 Sample size and basis for calculation

The estimated sample size was based on the objective response rate. The hypothesis of this study is that selmetinib sulphate can reduce the recurrence rate of patients after NF 1. The study parameters were set: α =0.025 (unilateral), Power=80%, and progression-free survival (PFS) in 20% of patients with NF 1 for 24 months. More than 50% of progression-free survival (PFS) in NF 1 patients.17 cases were calculated using PASS 15.0 software, considering 10% shedding rate, 19 subjects should be included.

.5.52 Data analysis set (e. g. full analysis set, compliance protocol set, safety analysis set)

Statistical analysis will be performed using the SAS statistical software (V.9.4, SAS Institute) Statistical analysis software for calculation, if no special instructions, the main indicators use one-sided test, control the first class error α is 0.025, the remaining indicators use two-sided test, one class error is α =0.05. To calculate confidence intervals, calculate two-sided 95% confidence intervals if not otherwise specified.

(1) Full analysis set (full analysis set, FAS): consisting of all subjects who received at least one drug / treatment and obtained efficacy assessment. This dataset was derived from all subjects after removing subjects in the least and reasonable way.

(2) Safety analysis set (safety analysis set, SS): a population treated at least once / once and having at least one safety evaluation data. In the safety analysis, all patients will be analyzed by the actual drug group.

(3) Compliance with the protocol set (per-protocal set, PPS): all concomitant medications that met the trial protocol and did not use the

impact effectiveness evaluation, good medication compliance (between 80% and 120%), excluded subjects who had major protocol violations and were judged to have a significant impact on the results. All protocol deviations causing the exclusion of subjects from the compliant protocol set will be described in detail in the Statistical Analysis Plan (SAP) and completed prior to data lock.

5.3 5 Statistical analysis plan

Data description of statistical analysis, analysis method of primary / secondary indicators / safety indicators, statistical school positive method, control of bias, stratification / subgroup / sensitivity analysis, etc

Demographic, and other baseline characteristics

Based on the analysis of FAS set, the demographic data, medical history, vital signs and other baseline data were statistically described, where the measurement data (age, BMI, XX, etc.) gave mean, SD, minimum, maximum, median, and gave frequency and corresponding percentage for count data (gender, XXX, etc.).

Analysis of efficacy indicators

(1) Main efficacy indicators

Point estimates for the main evaluation index (PFS) and estimated two-sided 95% confidence intervals using the Clopper-Pearson exact probability method. If the lower limit of the 97.5% confidence interval is greater than the proportion of 24 months, the treatment group was considered better effective than the historical control.

We obtained the analysis model:

$$Y = b_0 + b_1 \cdot X_1 + b_2 \cdot X_2 + b_3 \cdot X_3 + \epsilon$$

In this equation, the X_iRepresents the extent of tumor resection,

X_2Represents the solid tumor size, X_3Indicates the medication dose.b_0Is the intercept, b_1, b_2, b_3Is the regression coefficient of each factor, and the ϵ is the error term.

(2) Secondary efficacy indicators: analysis using FAS and PPS analysis sets. For survival measures, the digit survival time and its two-sided 95% confidence intervals were calculated. For the rate of each index, point estimates were performed and two-sided 95% confidence intervals were estimated using the Clopper-Pearson exact probability method. For the continuity index, the mean and two-sided 95% confidence intervals were calculated based on the normal distribution method, otherwise, the median and two-sided 95% confidence intervals were calculated based on the percentile method.

Safety index analysis

The SS set describes the incidence of adverse events / serious adverse events and adverse reactions, and lists the details of each adverse event in each subject, including the type and severity of adverse events. Safety and evaluation of laboratory indicators, vital signs, electrocardiogram and other safety related indicators, compare and evaluate the changes before and after treatment, and give statistical description of clinical evaluation (normal, abnormal without clinical significance, abnormal with clinical significance, not checked) before and after treatment.

Principles of handling of missing / deleted / lost to follow-up data

Main index analysis adopts LOCF (last observation carried forward) method, that is, the main index data is not observed at the last time; the secondary indicators and safety indicators are not filled.

6. Research intervention*

6.1 Study intervention content (description of intervention content, implementation steps, dose and route of intervention drug, frequency of intervention, product of test group and control group, etc.)

All patients received oral selmetinib hydrosulphate capsules (20-50mg bid) daily for 30 days for 6 cycles, based on individualized patient body surface area (BSA).

6.2 Preparation / handling / storage / responsibilities (drug versus control article allocation plan when intervention should be specified)

The use of drugs must be recorded in the patient's medical record and in the corresponding location of the CRF. After the enrollment of the subjects and at the 1 and 2 months of follow-up, the executive nurse shall receive the corresponding number of drugs at the drug administrator, and the remaining drugs and boxes shall be returned to the drug administrator. If the drug is found or damaged during the preparation process, this box of drugs should not be used, the damaged drugs shall be treated as empty bottles, and other undamaged drugs shall be returned to the drug administrator together with the packaging box. The study center shall be responsible for the management of test drugs, including receiving, distribution, counting and recovery. The investigator shall ensure that the test drug is stored in a safe, independent and locked place at the study site and the storage conditions shall meet the storage requirements of the test drug. No one can be contacted without the consent of the investigator. Empty boxes shall be stored and managed as the test drug.

6.3 Study Intervention Compliance (How to maintain, evaluate, and verify study compliance)

After each medication, the subject should be required to return to the study center for review, and the compliance of the study can be verified according to the subject's review. During the late follow-up, the study team members must conduct a telephone follow-up communication

with the subject and reasonably arrange the review visit.

6.4 Concomitant therapy (permitted adjuvant medication, complementary / replacement therapy)

If the subject has hypertension, diabetes, coronary heart disease and other diseases that need long-term drug control, the investigator and the relevant specialist should evaluate the impact of the disease and the relevant study protocol and determine the dose and duration of adjuvant medication.

6.4.1 Rescue (drug, treatment methods, relevant records.....)

The life hazards during the implementation of the clinical study protocol should be implemented in accordance with the clinical rescue plan, such as cardiopulmonary resuscitation, emergency airway management, emergency surgical treatment, relevant records during hospitalization should be recorded in the medical record system, after discharge should be recorded in the adverse event record form, and the investigator should analyze whether the rescue causes are related to the study and discuss and discuss synchronously in the rescue records.

7. Discontinuation of the study intervention / subject discontinuation and withdrawal*

7.1 Study Intervention discontinuation (reasons / criteria: such as how many adverse events occurred, length of study discontinuation, how data were collected during discontinuation and how to reactivate the study intervention, whether follow-up was continued during discontinuation)

If the Grade 5 adverse event of CTCAE 5.0 standard reaches 10% of the number of subjects, the study should be discontinued and the drug safety of the study protocol should be discussed to determine whether to adjust the dose of drugs in the study protocol, continue the follow-up during the study suspension, and maintain the follow-up record of the original

subject.

7.2 Subjects discontinuation / withdrawal from the study (possible reason for subject discontinuation; involving implantable device, discuss how to remove / replace, obtain alternative materials, later contact with the subject, etc.)

When the subject stops or withdraws from the study due to dissatisfaction with the treatment effect of the study plan or his own economic reasons, he should actively communicate with the subject, encourage the subject to actively treat and help them apply for public welfare funds to complete the treatment. If the subject clearly withdraws, the investigator can continue to complete the follow-up without the study intervention.

7.3 Loss to follow-up (measures to reduce and reduce missing data due to loss to follow-up)

The investigator should keep the contact information of multiple subjects and the contact information of the family members after the subjects are enrolled. The investigator should actively contact the subjects by phone after leaving the hospital, timely understand the condition and arrange the subject to the hospital in advance for the next stage of treatment.

8. Adverse events and unexpected events

Adverse events (AEs) are adverse medical events occurring after the subject receives the treatment, but they are not necessarily causally related to the treatment. An adverse event can be any adverse and unexpected signs (including abnormal laboratory findings), symptoms, or illness associated to the use of treatment, regardless of relation to treatment. It includes, but is not limited to,:

(1) the exacerbation of the preexisting disease before the use of the study treatment measures;

(2) The frequency or severity of seizure events increased before the use of study treatment;

(3) Abnormal changes detected or diagnosed after the use of the study treatment measures, although such abnormal changes may have existed before the treatment;

(4) deterioration of disease or symptoms that persisted before the study.

Causal relationship between adverse events and treatment measures: In the trial, the investigator should make a comprehensive analysis according to the specific situation of adverse events and the past history, concomitant diseases and concomitant medication to judge the relationship between adverse events and treatment measures. The relationship between adverse events and treatment measures is divided as "definitely related, most likely related, likely related, possibly unrelated and unrelated".

None: Adverse events were not associated with treatment measures.

Probably unrelated: The occurrence of adverse events is more likely related to other factors such as medication or concomitant

Disease, or the timing of the event suggests that it is unlikely to be causally related to treatment measures.

Possible concern: Adverse events may be caused by therapeutic measures. Cannot exclude whether it may be caused by other

Factors, such as: medication conditions or concomitant diseases. The occurrence of adverse events and treatment measures have a reasonable time order, and the causal relationship between events and treatment measures cannot be excluded.

It is likely that: adverse events may be caused by treatment measures. There is a reasonable temporal sequence of event occurrence and treatment measures.

Positive concern: The type of adverse event has been identified as

treatment and no other reason

Explanation, such as: medication status and concomitant diseases. The timing of the event strongly suggests causality.

Event severity criteria can be according to the Common AE evaluation criteria version CTCAE 5.0 (US Department of Health and Human Services). Beyond the above criteria list, refer to the following criteria:

Mild: Symptoms or signs but tolerable.

Moderate; discomfort enough to interfere with normal life.

Severe: Normal activities are already impossible.

All information about adverse events, whether mentioned by the patient, found by the investigator, or found by physical examination, laboratory examination, etc., should be recorded on the study medical record and case report form. During the trial, the time, duration, symptoms, signs, severity, measures taken, outcome and relationship assessment of adverse events should be carefully observed and recorded, and the results should be appropriately followed up.

Possible adverse events include: medication-related complications; procedure-related complications; and related complications after withdrawal.

The investigator should use medical terms / concepts to record AEs or SAEs. Its type, degree, occurrence time, duration, treatment measures, treatment are recorded in detail. The association of the combination of complications and medication with the study treatment was evaluated. All AEs (including SAEs) should be recorded on the Adverse Event Form for the CRF. Any patient who is treated must be evaluated for toxicity. The occurrence of any adverse events (AEs) should be graded according to the NCI Common AE classification criteria (NCI-CTCAE version 5.0).

9. Data collection and management

9.1 Case report form / electronic data records

Prior to the start of the study, the Redcap electronic database / EDC database was established based on the content of the paper version of the case report form.

9.2 Data management (data collection form, data storage carrier: electronic / paper, data integrity inspection, database establishment method, data management system, data quality detection method, definition of data lock library, etc.)

The original data should be uniformly recorded in the study medical records. According to the content of the study medical record, the case report form can be completed in the electronic database to ensure the integrity and accuracy of the information. In order to ensure the accuracy of the data, the researcher shall conduct self-examination no less than twice a year, regularly appoint personnel to the sub-center for project quality control, and accept the examination by the hospital and school management departments. If the data registered in the case report form / electronic database are inconsistent with the original records (study medical records), the investigator shall organize timely verification of the data, modify the wrong part according to the requirements of GCP regulations, and make corresponding explanations if necessary.

10. Ethics requirements

This study complied with the provisions of Good Clinical Practice and the Administration of Investigator-Initiated Clinical Studies (Trial) and the Declaration of Helsinki. This study will be conducted only before the ethical committee of the trial. In the course of the study process, the revised protocol must be resubmitted to the Ethics Committee for review, and the investigator must wait until the consent of the Ethics Committee before implementing the new protocol.

Each enrolled patient must sign an informed consent form. Copies of the informed consent form and contact information of the investigator and the ethics committee must be provided to the requested patients*. This study will collect the clinical data and personal information of the research subjects for scientific research, which will involve the privacy rights of the patients. The study participants and data analysts signed a confidentiality agreement not to disclose patient personal information and disease-related information to any individuals and institutions unrelated to the study. The collected patient data should be managed to prevent personal privacy leakage.

11. References

1. Ly KI, Blakeley JO.The Diagnosis and Management of Neurofibromatosis Type 1. Med Clin North Am.2019;103(6):1035-1054. doi:10.1016/j.mcna.2019.07.004
2. Gutmann DH, Ferner RE, Listernick RH, Korf BR, Wolters PL, Johnson KJ.Neurofibromatosis type 1. Nat Rev Dis Primers.2017;3:17004. Published 2017 Feb 23. doi:10.1038/nrdp.2017.4
3. Di Rocc C, Samii A, Tamburrini G, Massimi L, Giordano M.Sphenoid dysplasia in neurofibromatosis type 1: a new technique for repair [published correction appears in Childs Nerv Syst.2017 Dec;33(12):2211. Concezio DR [corrected to Di Rocc C], Amir C [corrected to Samii A], Gianpiero T [corrected to Tamburrini G], Luca M [corrected to Massimi L], Mario G [corrected to Giordano M]].Childs Nerv Syst.2017;33(6):983-986. doi:10.1007/s00381-017-3408-z
4. Miller DT, Freedenberg D, Schorry E, et al.Health Supervision for Children With Neurofibromatosis Type 1. Pediatrics.2019;143(5):e20190660. doi:10.1542/peds.2019-0660
5. Blakeley JO, Plotkin SR.Therapeutic advances for the tumors associated with neurofibromatosis type 1, type 2, and schwannomatosis.Neuro Oncol.2016;18(5):624-638. doi:10.1093/neuonc/nov200

6. Friedrich RE, Schmelzle R, Hartmann M, Fünsterer C, Mautner VF.Resection of small plexiform neurofibromas in neurofibromatosis type 1 children.World J Surg Oncol.2005;3(1):6. Published 2005 Jan 31. doi:10.1186/1477-7819-3-6
7. Prada CE, Rangwala FA, Martin LJ, et al.Pediatric plexiform neurofibromas: impact on morbidity and mortality in neurofibromatosis type 1. J Pediatr.2012;160(3):461-467. doi:10.1016/j.jpeds.2011.08.051
8. Gross AM, Singh G, Akshintala S, et al.Association of plexiform neurofibroma volume changes and development of clinical morbidities in neurofibromatosis 1. Neuro Oncol.2018;20(12):1643-1651. doi:10.1093/neuonc/noy067
9. Martin S, Wolters P, Baldwin A, et al.Social-emotional functioning of children and adolescents with neurofibromatosis type 1 and plexiform neurofibromas: relationships with cognitive, disease, and environmental variables.J Pediatr Psychol.2012;37(7):713-724. doi:10.1093/jpepsy/jsr124
10. Ferner RE, Huson SM, Thomas N, et al.Guidelines for the diagnosis and management of individuals with neurofibromatosis 1. J Med Genet.2007;44(2):81-88. doi:10.1136/jmg.2006.045906
11. Anderson MK, Johnson M, Thornburg L, Halford Z.A Review of Selumetinib in the Treatment of Neurofibromatosis Type 1-Related Plexiform Neurofibromas.Ann Pharmacother.2022;56(6):716-726. doi:10.1177/10600280211046298
12. Harder A.MEK inhibitors - novel targeted therapies of neurofibromatosis associated benign and malignant lesions.Biomark Res.2021;9(1):26. Published 2021 Apr 16. doi:10.1186/s40364-021-00281-0
13. Campagne O, Yeo KK, Fangusaro J, Stewart CF.Clinical Pharmacokinetics and Pharmacodynamics of Selumetinib.Clin Pharmacokinet.2021;60(3):283-303. doi:10.1007/s40262-020-00967-y
14. Gross AM, Wolters PL, Dombi E, et al.Selumetinib in Children with Inoperable Plexiform Neurofibromas [published correction appears in N Engl J Med.2020 Sep 24;383(13):1290].N Engl J Med.2020;382(15):1430-1442. doi:10.1056/NEJMoa1912735

15. Dombi E, Baldwin A, Marcus LJ, et al.Activity of Selumetinib in Neurofibromatosis Type 1-Related Plexiform Neurofibromas.N Engl J Med.2016;375(26):2550-2560. doi:10.1056/NEJMoa1605943