Oncolytic Virus Ad-TD-nsIL12 for Primary Pediatric Diffuse Intrinsic Pontine Glioma

Informed Consent Form (Guardian Version)

Part I. Notice to Legal Guardians

Dear Parent or Legal Guardian,

This informed consent form will describe a clinical trial that is part of a type of study. Your child will be invited to participate in this clinical study, and as a researcher, we will explain the study to you and your child. Minors participating in this study must obtain the consent of their parents or legal guardians, and this informed consent form provides you and your child with information to help you and your child decide whether to participate in this clinical study. Please read it carefully and ask the researcher in charge of the study if you have any questions.

This study has been obtained, and some of the content covered in this article is determined by regulatory requirements, and this study has been approved by the Ethics Committee of Sanbo Brain Hospital affiliated to Capital Medical University (grant number: SBNK-YJ-2022-020-02).

We planned to include between 9 and 18 participants.

1. What is "given consent"?

Your child's participation in this study is voluntary, so it is up to you to decide whether you would like your child to participate in this study. If you agree to have your child participate, you must sign at the end of this document to indicate your consent to your child's participation in this study. This process is known as "giving consent".

Please complete the following steps before making a decision:

(1) the researcher has introduced you and your child to the study;

(2) you and your child have understood the purpose and risks of the study;

(3) You and your child are willing to cooperate with the relevant requirements of this study.

2. Who do I contact if I or my child have any questions?

If you and your child have any questions or concerns about this study, you can consult Dr. Ning Weihai or Dr. Qian Xiao who is in charge of this study at 13161256767/18020295435.

If you and your child have any questions about their right to participate in this study, please contact the Ethics Committee of Sanbo Brain Hospital at 010-62856956/6798.

3. Why is this study being conducted?

Background: Diffuse intrinsic pontine glioma (DIPG) is a disease associated with histone mutations and a leading cause of death associated with brain tumors in children. Due to the specificity of the location of the tumor and the high infiltration of the tumor itself, the current treatment options for this disease are very limited. Despite the short-term benefit of standardized radiotherapy in the treatment of DIPG, the prognosis remains poor, with patients often presenting with progressive neurological deterioration, median survival less than 1 year,

and 2-year survival rates less than 10%. Due to the severe lack of treatment for DIPG, it is imperative to seek a variety of emerging treatments, including oncolytic viruses.

Over the past 20 years, molecular and genetic tools have been available to build new viruses that transfer exogenous genes into cancer cells. The initial study used viral vectors with replication defects to deliver various genes to target tissues. These gene therapies have also shown efficacy and safety in multiple preclinical tumor animal models. However, these promising preclinical results have not been successfully translated into patient benefit in clinical practice. This defect is largely due to the inability of viral vectors to transform cancer cells in large numbers. Typically, these vectors infect only a small number of cells in the body, and in the best case no more than 15%. With the development of molecular biology and genetic engineering technology, the use of a variety of differences between tumor cells and normal cells to construct viruses that can selectively replicate in tumor cells, use the rapid replication of viruses in tumor cells, lead to tumor destruction, and release viruses to continue to infect new tumor cells, that is, oncolytic virus therapy. This method was first developed and utilized in herpesviruses. In recent years, many other oncolytic viruses with the ability to replicate have been developed. Adenoviruses (AdV) are particularly well-suited to this approach because they cause the least disease in humans and can be genetically manipulated to infect and replicate in dividing and non-dividing cells. A variety of highly replicable AdV has been shown to be safe in clinical trials. E1B-55K and E3B gene deletion adenovirus type 5 (Ad5) H101 is the first international oncolytic virus product approved by China in 2005. Similarly, recombinant replicating active AdV, containing multiple gene deletions, has been produced, and their effectiveness as therapeutic agents has been validated in vivo and in vivo models of many primary and metastatic tumors. These animal model-based experiments provide valuable information about the effectiveness and safety of the virus. Experiments have clearly demonstrated that by altering these genes, whether through deletion, insertion, or point mutation in coding regions, the resulting virus will kill dividing tumor cells but is non-toxic after delivery to normal brain tissue.

Therefore, it is possible to develop an ideal, stable genetically engineered virus to selectively kill glioma cells. The brain is an immune "exempt" area, which is also a reason for the poor treatment effect, rapid development and poor prognosis of brain tumors, which is an advantage of oncolytic virus therapy. Therefore, brain tumors are suitable targets for intervention by oncolytic viruses, which use conditionally replicated viruses to replicate in tumors and kill tumor cells while preserving the normal cell population in the brain. In recent years, some clinical trials of oncolytic viruses for the treatment of brain tumors have shown good treatment prospects.

Objective: To observe the safety, tolerability and efficacy of Ad-TD-nsIL12 intratumoral injection in pediatric DIPG patients.

4. How was the study conducted?

4.1 Time of screening

Patients will be screened at the clinic by the trial's researchers. Screening will be performed within 15 days prior to the use of Ad-TD-nsIL12. Prior to screening, investigators will present

parents and subjects with complete information about the clinical study and sign an informed consent form. Registration for trials can only be performed if the following screening trials have been conducted and the inclusion and exclusion criteria have been met:

- Physical examination, including vital signs and weight.
- Neurological examination and functional status assessment.
- Quality of life assessment (PedsQL$^{TM)}$.
- Clinical laboratory tests, including hematology, chemistry (containing C-reactive protein), and coagulation.
- Detection of adenovirus antigens and antiadenovirus antibodies in serum.
- Pregnancy test (serum).
- Serological testing for HIV and hepatitis B virus/hepatitis C virus.
- MRI (with or without gadolinium).
- Drug use.

To reduce subsequent attrition bias, participants will be asked to provide contact details of two or more relatives.

4.2 In-hospital treatment

Follow-up 0: Duration: 3±1 days after Ad-TD-nsIL12 injection. Includes the following:

•Physical examination, including vital signs, weight, and height;

• Neurological examination and functional status assessment (LPS or KPS), quality of life assessment;

•Blood tests, blood biochemistry (containing C-reactive protein), coagulation assessment, and other blood tests (including tests).

Detection of adenovirus antigens and antiadenovirus antibodies in serum);

•MRI (with or without gadolinium) and tumor response assessment;

• Evaluation and documentation of adverse events, including concomitant medications, including steroids;

• stereotactic biopsy and administration of Ad-TD-nsIL12;

• Tumor tissue acquisition and processing.

After stereotactic biopsy, an Ommaya capsule will be inserted through the biopsy channel and a single injection of Ad-TD-nsIL12 will be given immediately after surgery.

If the subject presents with symptoms of decreased brain function or decreased cardiovascular perfusion, or if there is an allergic reaction or signs of anaphylaxis, administration of Ad-TD-nsIL12 should be discontinued. In addition, treatment of Ad-TD-nsIL12 will also be discontinued in the event of other adverse events deemed necessary by the investigators.

The tumor tissue obtained at the time of biopsy or excision, as well as the blood samples obtained, will be archived in our hospital for future analysis.

When the patient is discharged, the subject and his or her relatives will be provided with the investigator's contact information to outside caregivers and medical staff in the event of an emergency. In addition, after discharge, the patient can follow the recommendations of his/her

pediatric oncologist for treatment in other hospitals, and the investigators of the experimental group will contact the hospital for follow-up visits.

Radiation therapy will be started 2-6 weeks after the biopsy and virus injection at the discretion of the radiation therapist.

4.3 Planned clinical follow-up

After inclusion in the studies, clinical follow-up will be conducted every 4 weeks for the first 3 months after viral treatment. After 3 months, follow-up visits can be performed by phone, images and blood tests can be sent by email, or patients can come to our hospital for treatment and follow-up if they wish. Treatment tolerability was measured by severity grading of adverse events and correlation with the drug in question.

Follow-up 1: Duration: 28±5 days after Ad-TD-nsIL12 injection. The assessment is as follows:

•Physical examination, including vital signs, weight, and height.

• Neurological examination and functional status assessment (LPS or KPS);

• Quality of Life Assessment (PedsQL$^{TM)}$;

• Laboratory blood tests, some of which will be retained for subsequent analysis;

•MRI (with or without gadolinium) and tumor response assessment;

• Evaluation and documentation of adverse events, concomitant medications;

• Steroid evaluation.

Follow-up 2: Duration: 8±1 weeks after Ad-TD-nsIL12 injection. The assessment is as follows:

•Physical examination, including vital signs, weight, and height.

• Neurological examination and functional status assessment (LPS or KPS);

• Quality of Life Assessment (PedsQL$^{TM)}$;

• Laboratory blood tests, some of which will be retained for subsequent analysis;

•MRI (with or without gadolinium) and tumor response assessment;

• Evaluation and documentation of adverse events, concomitant medications;

• Steroid evaluation.

Follow-up 3: Duration: 12±1 weeks after Ad-TD-nsIL12 injection. The assessment is as follows:

•Physical examination, including vital signs, weight, and height.

• Neurological examination and functional status assessment (LPS or KPS);

• Quality of Life Assessment (PedsQL$^{TM)}$;

• Laboratory blood tests, some of which will be retained for subsequent analysis;

•MRI (with or without gadolinium) and tumor response assessment;

• Evaluation and documentation of adverse events, concomitant medications;

• Steroid evaluation.

Follow-up 3 is the final planned clinical follow-up, after which overall adverse events will be discussed and assessed for the patient.

With the exception of the 3 planned follow-ups, both patients and investigators may request unplanned follow-up and have examinations as needed.

During follow-up, if viral transmission of the CSF is considered in the patient, the investigator will decide whether to perform virological (AdV) testing.

4.4 Long-term follow-up

Duration of long-term follow-up: (6 months± 1 month, 12 months± 1 month, 18 months± 1 month, 24 months± 1 month), follow-up content (telephone, video, or outpatient treatment):

• whether it is alive or not;

• Quality of life assessment;

• Evaluation and documentation of adverse events, concomitant medications;

• Assessment of steroid use;

•If any imaging tests are performed, radiological information is collected and analyzed.

After that, patients will continue to receive standardized treatment with DIPG, and investigators will continue to follow up with basic information, including but not limited to survival, quality of life, and occurrence of adverse events. Depending on the special and necessary clinical situation, the investigator may request increased follow-up frequency, or even follow-up in the hospital.

At the time of tumor progression, the study will end, the patient and their guardians will decide on follow-up treatment at their own discretion, and the investigator will continue to collect basic information about clinical status (including at least whether the patient is alive and quality of life assessment) through follow-up until the study subject dies or the virus is injected for at least 2 years.

If the tumor does not progress, the investigators will continue to collect basic information about the clinical status (including, at a minimum, whether the patient is alive and quality of life assessment) through follow-up until the study subject dies or the virus is injected for at least 5 years. Again, researchers can decide at any time to conduct a final analysis of the study data or to continue long-term follow-up of certain subjects, a decision that can only be made after all subjects have died or been followed for more than a year.

4.5 Follow-up of laboratory tests

Basic blood tests will be done before, early (within 3 days), and during 1 to 3 visits. These tests will include, but are not limited to:

•Hematology: White blood cell count with differential, including neutrophils, lymphocytes, monocytes, eosinophils and basophils, red blood cell count, hemoglobin, hematocrit, platelets, mean platelet volume (MPV), MCV, MCH, MCHC, RDW.

•Chemical and C-reactive proteins: glucose (fasting), creatinine, sodium, potassium, chloride, calcium and C-reactive proteins.

•Coagulation: PT, APTT

4.6 Follow-up of radiology

MRI will be used to track tumor response, and assessment of tumor reflection requires the use of a uniform sequence from baseline (T2 or enhanced recommended). Time of check:

• within 15 days before viral treatment;

• within 3 days after viral treatment;

•follow-up 1 (28±5 days after Ad-TD-nsIL12 injection);

•follow-up2 (8±1 weeks after Ad-TD-nsIL12 injection);

•Follow-up 3 (12±1 weeks after Ad-TD-nsIL12 injection).

Researchers can request an MRI at any time during the study to determine the imaging response of the tumor. **5. Are there other treatment options for my child?**

Participation in this study may or may not improve your child's health. Your child can skip the study and continue with the doctor's usual care.

6. What does my child need to do in the study?

Provide factual information about your medical history and current medical condition; Tell the study physician about any discomfort your child experienced during the study; Tell the study doctor if your child has recently participated in other studies or is currently participating in other studies.

7. What are the risks and adverse effects of my child's participation in this study?

7.1 Risks associated with Ad-TD-nsIL12 therapy

Ad-TD-nsIL12 can cause, or is likely to cause, the following;

•Systemic viral infections, such as flu-like symptoms (chills, stiffness, myalgia, arthralgia, lymphadenopathy);

•Allergic reactions to the virus, such as itching, hives, changes in blood pressure, or difficulty breathing respiratory infections;

•Brain infections;

•Hepatitis, which may present with abdominal pain, jaundice, and abnormal liver function tests.

Ad-TD-nsIL12 has been carefully designed to reduce its ability to produce toxic effects, but side effects are still possible. If there are signs of neurotoxicity associated with Ad-TD-nsIL12 infection, supportive care and medical treatment will be implemented as needed. Cerebrospinal fluid cultures, and other appropriate tests may be obtained if possible in participants with evidence of neurotoxicity. Neurotoxic effects, if they occur, may be short-lived; However, permanent damage is also theoretically possible. As with any clinical trial, unforeseen risks are possible. In China, many people have been exposed to AdV before and already have antibodies. If subjects treated with Ad-TD-nsIL12 have never been exposed to AdV before, they may develop antibodies during the study. Although the effects of wild-type AdV on the developing embryo or fetus are known and may cause miscarriage, fetal death, fetal infection, or developmental abnormalities, there are no data on the effects of Ad-TD-nsIL12 in utero. Ad-TD-nsIL12 may enter the fetus through the placenta. Therefore, all subjects and their partners are advised to use appropriate forms of contraception during their participation in this study and for 6 months after administration of Ad-TD-nsIL12. Women suspected of pregnancy during the study and needed to be checked for pregnancy status at any time.

Treatment of concurrent severe viral infection: confirmation of the presence of AdV

infection is important for deciding on antiviral use, ruling out other treatable infections, determining prognosis, and initiating infection control measures if appropriate. If serious AdV infection is suspected after administration of Ad-TD-nsIL12, laboratory investigations such as polymerase chain reaction (PCR) and culture, analysis of cerebrospinal fluid and serum to rule out AdV infection will be performed. Other diagnostic tests such as antigen measurement, serotyping, and serology may be indicated. Additional MRI scans and brain biopsies may also be needed to determine the presence of AdV. Ribavirin, ganciclovir, cidofovir, immunotherapy, or other antiviral therapy can be started immediately, followed by appropriate treatment of the subject.

7.2 Risks associated with treatment

•Biopsy

Prior to injection of Ad-TD-nsIL12, frozen sections of the tumor will be obtained to confirm the diagnosis of DIPG. When appropriate, if encephalitis is suspected, stereotactic biopsy may be performed to assess for the presence of Ad-TD-nsIL12 or wild-type AdV infection or, if necessary, to confirm tumor progression. Risks of brain biopsy include haemorrhage, haematoma, infection (local infection, brain abscess, meningitis), fever, pain, increased intracranial pressure, general decline in consciousness, focal neurologic deficits (e.g., weakness, loss of sensation, speech disturbance, aphasia, memory loss, loss of vision, diplopia, loss of cognitive function), seizures, stroke, coma, and death.

•Tumor resection

The risks associated with craniotomy and tumor removal are varied, including but not limited to pain, bleeding, bleeding, epilepsy, stroke, infection, fever, decreased level of consciousness, focal neurological deficits (eg, weakness, sensory loss, speech impairment, aphasia, memory loss, vision loss, diplopia, and any other deficit of brain function, complete or partial loss of cognitive function), coma, and death. In addition, there are non-neurologic risks that can arise from any surgery or anesthesia (including, but not limited to, respiratory failure, pneumonia, cardiac arrest, myocardial infarction, pulmonary embolism, deep vein thrombosis).

•MRI

Risks associated with MRI include claustrophobia and anxiety reactions. Reactions to the contrast medium gadolinium include; Nausea, headache, hot flashes, and palpitations. Allergic reactions to gadolinium include: skin rash, urticaria, dyspnea, in extreme cases, anaphylactic shock and possible death. Individuals with any contraindications to MRI (e.g., pacemakers, epicardial pacemaker lines, infusion pumps, surgical and/or aneurysm clips, shrapnel, metal prostheses, potentially magnetic implants, metal objects in the eye, etc.) will not be included. In addition, individuals with tumors that cannot be assessed by MRI will not be eligible for the study.

•Encephalitis

Postoperative fever is not uncommon. However, fever of ≥ 38.9°C (with or without seizures) lasting ≥ 48 hours, decreased neurologic status on MRI, and increased areas of hemorrhagic

necrosis outside the tumor boundary may indicate viral encephalitis. When appropriate, stereotactic biopsy should be performed to determine the presence of Ad-TD-nsIL12 or AdV (wild-type). The procedure of a biopsy involves taking a sample of tumor tissue through a biopsy needle and sending it to a hospital laboratory for testing. Biopsy specimens undergo standard hematoxylin and eosin (H&E) staining, as well as immunostaining. In addition, if the specimen is sufficient, tests such as PCR and culture to detect AdV and Ad-TD-nsIL12 will be performed. The pathologist will review the processed biopsy tissue. Antiviral therapy is given as appropriate.

•Focal neurologic deficits

Decreased neurological status (eg, decreased mental status), including focal neurologic deficits or specific neurologic deficits (paralysis, speech impairment, depending on tumor location), can be attributed to tumor progression, edema, haematoma, hydrocephalus, or encephalitis. CT and, if appropriate, MRI to help determine the cause of these neurological changes.

•Bleeding

PT/INR, PTT, and platelet count are measured. Small hematomas can be observed conservatively. Large haematomas or hematomas associated with progressive neurological deterioration (i.e., CTC > grade 3) may require surgical hematoma removal and decompression. The acceptable degree of neurotoxicity secondary to hematoma is (CTC < grade 3).

•Increased intracranial pressure

Symptoms in patients with mass masses may be related to increased intracranial pressure. Symptoms may worsen, especially after an injection of Ad-TD-nsIL12. For more extreme cases, standard treatment includes dexamethasone or mannitol

•Necrotizing meningitis

Response to Ad-TD-nsIL12 may cause inflammation or meningeoid symptoms. Symptoms may be self-limited and controlled with steroids and/or analgesics, but in some cases may be severe enough to cause nerve damage or death. To exclude infection, it may be necessary to perform a lumbar puncture.

•Cerebral edema

Cerebral edema usually occurs postoperatively in patients with tumors and usually requires standard measures to treat elevated intracranial pressure. Edema may be secondary to the disease process, surgical process, necrosis and inflammation, viral particles, metastatic tumor cells. Symptoms may include, but are not limited to, severe headache, confusion, lethargy, unresponsiveness, or focal neurological deficits. Participants generally take prophylactic high-dose steroids, but the dose may need to be increased. Edema that does not respond to aggressive treatment can lead to permanent nerve damage.

•Infection

Any surgical procedure carries a risk of infection. This risk may be increased by injecting the virus.

•Other risks: Description of possible risks by taking a history of risks: For example, it may be

psychologically uncomfortable for your child to communicate and talk to us.

Risks and discomforts that may be caused by predicted and unpredicted adverse reactions of the test drug, and examinations during the test.

If the subject experiences any discomfort in the study, or a new change in the condition, or any unexpected situation, whether related to medications/examinations or not, the attending physician of the subject should be contacted in a timely manner, and the doctor will make a judgment and medical treatment on this.

If any trial-related damages occur as a result of participation in the trial, subjects will receive prompt treatment and corresponding compensation.

8. What are the benefits of this research for my child?

Participation in this study may make the tumor stop growing for a certain period of time, or shrink, or even disappear completely, so that the health status improves; It is also possible that treatment fails and will not make your child's health better. The relevant research information and results obtained from this research will be communicated to you and your child in due course.

9. Will I be paid to participate in the study?

Your child will not receive any compensation for participating in this trial or this study.

10. Do I have to pay anything to participate in the study?

Your child's participation in the project does not need to pay the expenses incurred in the preparation of Ad-TD-nsIL12, equipment fees (equipment purchase fees, trial production equipment fees, equipment modification fees, equipment rental fees), labor fees, expert consultation fees, conference/travel/international cooperation exchange fees, material fees, testing and laboratory processing fees, fuel power fees, publication/documentation/information dissemination/intellectual property affairs fees required for the implementation of the project. In addition, you will pay for the normal medical expenses of laboratory fees, examination fees, hospitalization fees, etc. related to the treatment of the disease.

11. What should I do if my child is harmed while participating in the study**?**

If a medical emergency occurs in the patient in the study, seek medical attention to the nearest emergency department and contact the patient's attending physician. If the patient develops an illness or injury in the course of participating in the research project that is not directly related to the research project, the cost of such treatment is borne by the patient. Physicians will do their best to prevent and treat possible harm as a result of this study. This trial has purchased clinical trial insurance for the subjects, and if an adverse event occurs in the clinical study, the medical expert committee will determine whether it is related to the treatment of Ad-TD-nsIL12, and provide the cost of treatment and corresponding economic compensation for research-related damage in accordance with the provisions of China's "Good Clinical Practice for Clinical Trials". Treatment and testing required for other concurrent conditions will not be free of charge.

Even if you have signed this informed consent form, you retain all your statutory rights.

12. Will my child's information be kept confidential?

Your child's medical records will be kept in the hospital, and the investigators, research authorities, and ethics committee will be allowed to access your child's medical records. Any public report on the results of this study will not disclose your child's personal identity. We will make every effort to protect the privacy of your child's personal medical information to the extent permitted by law. Personal and medical information about your child will be kept confidential and kept in a safe and secure place. At any time, you can request access to your child's personal information (such as name and address) and amend it if necessary. By signing this informed consent, you consent to the use of your child's personal and medical information for the circumstances described above.

The research data will be stored in the form of written text and electronic files for 2 years after the end of the study, and the association code of the data and your child's privacy information will be kept by a safe place and double lock of the researcher's unit (department), and the storage place is Sanbo Brain Hospital affiliated to Capital Medical University.

We will contact you during the study with any meaningful new developments or medical information related to your child's health, such as advising your child to have a writing test to identify this new information. I will also keep you informed of any new information that may influence your choice to continue to enroll your child in the study.

13. Does my child have to participate in this study?

Whether or not to participate in the study is entirely up to you and your child's voluntariness. You and your child may refuse to participate in the study, or withdraw from the study at any time during the study, without affecting your contact with the doctor, or the loss of medical or other benefits to your child.

If your child needs additional treatment, or if your child does not follow the study plan, or if an injury-related injury has occurred or for any other reason, the study physician may terminate your child's continued participation in the study.

14. What will happen to my child's biological samples and medical information?

In addition to this study, it is possible to reuse your child's biological specimens and research data in future oncolytic-related studies, which will be coded (excluding private information that can be linked to you and your child) to ensure that you and your child cannot be personally identified by anyone who comes into contact with these samples and information. We will also make every effort to keep your and your child's personal information confidential to the extent permitted by law. You may also refuse to use your child's biological specimens and research data for studies other than this one.

Part II. Informed Consent Signature Page

Legal Guardian Statement:

I have read this PIC form and have discussed and asked questions with my doctor about this study. The doctor has explained to me in detail the purpose of the study, the research process, the possible risks and benefits, and answered all my questions, and I understand that participation in this study is voluntary.

I confirm that there is sufficient time to consider this, including the risks that may arise from participating in the study. I am also aware that if I withdraw from the study midway, especially when my child withdraws from the study due to treatment, I will inform the doctor of the change in time and complete the corresponding physical examination and physical and chemical examination, which will be beneficial to my child and the entire study. If my child needs any other treatment because of a change in his condition, I will seek advice from the doctor beforehand or tell the doctor truthfully afterwards.

My child and I Resources participated in this study. My child and I agree that the researcher, sponsor, health management supervision department/drug and food supervision department, and ethics committee will review my child's research materials. My children and I have also agreed to use the material again in the future for research on other similar topics.

I will be given a signed and dated copy of informed consent.

Subject's Name:_____

Signature of the legal guardian: _____Relationship with the child:_____

Date:_____

I (Signed) _____agree that the investigator will use my child's biological specimens and related data again after deleting my and my child's personal information in follow-up research related to this topic.

Subject's Name:_____

Signature of the legal guardian: _____Relationship with the child:_____

Date:_____

Investigator Statement:

I confirm that I have explained the details of the study, including its rights and possible benefits and risks, to the subject's guardian and given him a signed copy of informed consent.

Informed consent to talk to the signature of the doctor (investigator):_____

Date:_____

Contact Number:_____

Oncolytic Virus Ad-TD-nsIL12 for Primary Pediatric Diffuse Intrinsic Pontine Glioma

Informed Consent Form (Children Version)

Part 1 Information for Children

Dear children: Hello!

Because your parents feel that your recent dizziness and headache have affected your life, they took you to see a doctor today, and the doctor thought that your condition may be sick. It just so happens that our Department of Neurosurgery is conducting a clinical study of a new drug to treat your condition, and your doctor understands that your condition may be eligible, so he would like to invite you to participate.

This informed consent form is to inform you about the purpose of the study, what you should do during the study, your possible benefits and the discomfort you may feel. Please read carefully and decide whether to participate. You can consult with your parents (dad, mom or guardian) before making a decision. Your parents (dad, mom or guardian) will also have an informed consent form read and signed.

1. Why was this study conducted?

Your dizziness and headache have a great impact on your study and life, and other children have similar conditions and need to be treated by doctors. Ad-TD-nsIL12 is a drug under research and has not yet been approved for marketing in China. The objective of this study was to evaluate the efficacy and safety of Ad-TD-nsIL12.

2. How many children will participate in this study?

The study required about 9-18 children, with a total of 1 hospital participating.

3. How was the study conducted?

3.1 Research Methods

If you agree, you will be given the medication according to the dose arrangement of the group.

3.2 Dosage and method of administration

After a minimally invasive procedure, you will be given a small sac and Ad-TD-nsIL12 injections will be given after the surgery.

3.3 Arrangements for medical treatment

You will need to go to the hospital about every 3-5 weeks to have the doctor observe your treatment. When you are at home, you should also listen to your parents and measure your blood pressure and pulse rate on time. If there is anything uncomfortable, talk to your parents in time.

4. What do you need to do?

If you participated in this study, you need:

(1) Tell your doctor where you are unwell, or what diseases you have had before;

(2)Tell the doctor about any discomfort you have experienced during the study and the

medications you have taken, etc;

(4) Obtain the permission of a doctor to receive other drugs or treatments;

(5) Follow the doctor's guidance;

(6) If there is anything unclear, you can always ask the doctor or parents.

5. What are the benefits you may receive?

Your dizziness and headache may get better, but we can't guarantee that it will get completely better or not. We hope that the efficacy data from this study can be used in the future to help children with similar conditions to yours.

6. What discomfort may you feel?

All treatment drugs may have side effects, you may feel dizzy, drowsy, easy to exert, nausea, stomach pain, etc., please refer to the legal guardian's version of the "Informed Consent Form".

Drawing blood from your arm may feel a little painful, and sometimes there may be short periods of bruising and bruising.

Your doctor will pay attention to the side effects of the drug and ask you to cooperate with your parents to measure blood pressure and pulse rate. If you feel any discomfort, tell your teacher or parent immediately and ask them to tell the doctor, who will treat you as soon as possible.

7. Is it mandatory to participate in and complete this study?

Whether or not you participate in this study is entirely voluntary. If you don't want to, you can refuse to participate, which will not affect your access to treatment. After attending, you can change your mind at any time and tell the doctor to quit without affecting your treatment, and the doctor may provide advice and guidance based on your condition.

If this research plan changes, we will keep you and your parents informed. If you and your parents have any questions or concerns about this study, you can consult the doctor in charge of this study at 13161256767/18020295435. If you and your parents have any questions about your right to participate in this study, please contact the Ethics Committee of Sanbo Brain Hospital at 010-62856956/6798.

Part II Informed Consent Signature Page

Subject Informed Consent Statement:

I have understood the purpose of the research on Ad-TD-nsIL12 for the treatment of diffuse endogenous pontine glioma, what to do during the study, the possible benefits, and the discomfort that may be felt. I had plenty of time and opportunity to ask questions, and I was satisfied with the answers to them. I have read this informed consent form, I have discussed this research project with my parents, and I agree to participate in this study. I knew that at any point during the study I could withdraw from the study without any reason. I will be given a copy of this informed consent form containing the signatures of me, my guardian, and the research physician.

Subject Signature:_____ Date:_____

Guardian's signature:_____ Date:_____

Relationship with subjects:_____ Phone:_____

(Note: If the guardian is a parent, please sign both parents, if one of the parents does not show up, please call on the spot.)

Study Physician Notification Statement:

I have informed the subject of the background, purpose, steps, risks and benefits of Ad-TD-nsIL12 in the treatment of diffuse endogenous pontine glioma, and given him/her sufficient time to read the informed consent form and discuss it with others and answered their questions about research. I have informed the subject and his/her parents (guardians) contact details in case of problems. I have informed the participant that he/she can withdraw from the study at any time during the study without any reason.

Informed consent to talk to the signature of the doctor (investigator):_____

Date:_____

Contact number:_____