Cover Page

Release Date: July 16, 2025

ClinicalTrials.gov ID: NCT01064466

Unique Protocol ID: IND 178172 Commercial

Brief Title: Pharmacogenomics ANDA SNP Clinical Study - Etoposide and Single Nucleotide Polymorphisms (Drugs-SNPs)

Official Title: Explore the Relationship Between Single Nucleotide Polymorphisms and Etoposide Response and Toxicity in Patients with Small Cell Lung Cancer.

Secondary IDs: FWA00015357 [Registry ID: HHS, Human Protections Administrator]
NPI - 1831468511 [Registry ID: HHS, Health Care Provider Individual]
NPI - 1023387701 [Registry ID: HHS, Health Care Provider Organization]
IRB00009424 [Registry ID: IRB]
IORG0007849 [Registry ID: IORG]
IND178172 [Registry ID: FDA IND]

4. General Investigational plan [21 CFR 312.23(a)(3)]

Contents

21 CFR § 320.31

Applicability of requirements regarding an "Investigational New Drug Application."

21 CFR 320.31(a)

Any person planning to conduct an in vivo bioavailability or bioequivalence study in humans shall submit an "Investigational New Drug Application" (IND) if:

21 CFR 320.31(a)(3)

The study involves a cytotoxic drug product.

21 CFR 320.31(b)

Any person planning to conduct a bioavailability or bioequivalence study in humans using a drug product that contains an already approved, non-new chemical entity shall submit an IND if the study is one of the following:

21 CFR 320.31(b)(1)

A single-dose study in normal subjects or patients where either the maximum single or total daily dose exceeds that specified in the labeling of the drug product that is the subject of an approved new drug application or abbreviated new drug application.

21 CFR 320.31(c)

The provisions of parts 50, 56, and 312 of this chapter are applicable to any bioavailability or bioequivalence study in humans conducted under an IND.

21 CFR 312.23(a)(1)(v)

A commitment to conduct the investigation in accordance with all other applicable regulatory requirements.

Statement

I write the **statement** with respect to each clinical study involving human subjects that it either will be conducted in compliance with the institutional review board regulations in part 56 or will not be subject to the regulations under §56.104 or §56.105; and that it either will be conducted in compliance with the informed consent regulations in part 50 or will not be subject to the regulations under §50.23 and §50.24.

21 CFR §312.23 (a)(3)

(3) Introductory statement and general investigational plan.

(i) A brief introductory statement giving the name of the drug and all active ingredients, the drug's pharmacological class, the structural formula of the drug (if known), the formulation of the dosage form(s) to be used, the route of administration, and the broad objectives and planned duration of the proposed clinical investigation(s).

The name of the drug and all active ingredients:
ETOPOSIDE capsule (NDC 0378-3266-94) (ANDA075635) (Etoposide)

The drug's pharmacological class:
Antineoplastics (Oncology Drug)

The structural formula of the drug:
LABEL: ETOPOSIDE capsule (https://dailymed.nlm.nih.gov/dailymed)

The formulation of the dosage form(s) to be used:

Usual Approach Group
ETOPOSIDE capsule (NDC 0378-3266-94) (ANDA075635) -- 3 x 50 mg orally daily

Study Approach Group
China Import - ETOPOSIDE capsule (ANDA220887) -- 3 x 50 mg orally daily

The route of administration:

Usual Approach Group: Oral Administration = OS

Study Approach Group: Oral Administration = OS

The broad objectives of my proposed clinical investigation:

Explore the relationship between single nucleotide polymorphisms and etoposide response and toxicity in patients with small cell lung cancer.

The planned duration of my proposed clinical investigation:

90 days -- Phase 2 **ANDA SNP** Oncology Clinical Investigation

(ii) A brief summary of previous human experience with the drug, with reference to other IND's if pertinent, and to investigational or marketing experience in other countries that may be relevant to the safety of the proposed clinical investigation(s).

LABEL: ETOPOSIDE capsule (https://dailymed.nlm.nih.gov/dailymed)

(iii) If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal.

The drug (Etoposide) has **never** been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness.

(iv) A brief description of the overall plan for investigating the drug product for the following year. The plan should include the following: (*a*) The rationale for the drug or the research study; (*b*) the indication(s) to be studied; (*c*) the general approach to be followed in evaluating the drug; (*d*) the kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate); (*e*) the estimated number of patients to be given the drug in those studies; and (*f*) any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug or related drugs.

90 days -- Phase 2 **ANDA SNP** Oncology Clinical Investigation

(a) The rationale for the drug and the research study:

- The DNA gene chains are only formed by four types of nucleotides (Adenine = A; Thymine = T; Guanine = G; Cytosine = C). A single-nucleotide polymorphism (SNP) is a DNA sequence variation occurring a single nucleotide A, T, G, or C in a genome. Every SNP often has only two kinds of absolute different nucleotide composition forms, A<=>T or G<=>C. SNP is a dimorphic marker; if it is not A<=>T, it must be G<=>C; oppositely, if it is not G<=>C, it must be A<=>T. To almost all SNPs, every SNP is biallelic alleles, i.e., it only has two alleles as alternativa to all possible forms from all types of DNA nucleotides, A<=>T or G<=>C. Since every SNP should be a kind of ALL-OR-NONE gene mutation phenomenon, either it must have all, or it must have nothing all; this is almost same as the binary calculation of all computers, i.e., 0<=>1 mode.

- Because SNP biallelic alleles genetics mode is almost same as the computer binary (0<=>1) calculation mode, SNP is the most suitable for high throughput analysing based on computer software. The first-selection analytical method to discover novel SNPs and to detect known SNPs is DNA precisely sequencing. Through high-throughput DNA precisely sequencing, high-throughput DNA sequence comparing, and high-throughput DNA chain genotyping, any one SNP will surely be found based on computer software analysing. Based on related computer software, any one drug target gene SNP will surely be found via drug target gene DNA strands' high-throughput DNA precisely sequencing, high-throughput DNA sequence comparing, and high-throughput DNA chain genotyping.

- The single-nucleotide polymorphisms (SNPs) are usually biallelic alleles and thus easily assayed by high-throughput DNA precisely sequencing. The now most cutting-edge DNA sequencing approach is the Oxford Nanopore DNA Sequencing uses electrophoresis to transport an unknown sample through an orifice of 10^{-9} meters in diameter. A nanopore system always contains an electrolytic solutions - when a constant electric field is applied, an electric current can be observed in the system. The magnitude of the electric current density across a nanopore surface depends on the nanopore's dimensions and the composition of DNA or RNA that is occupying the nanopore. Sequencing is made possible because, when close enough to nanopores, samples cause characteristic changes in electric current density across nanopore surfaces. The total charge flowing through a nanopore channel is equal to the surface integral of electric current density flux across the nanopore unit normal surfaces between times t_1 and t_2. Oxford Nanopore DNA sequencing is referred to as "third-generation" - "high-throughput" - "long-read" DNA sequencing technology. This approach is currently the world's most simple and efficient SNP detection and the highest accuracy rate of the method. In SNP clinical trial design, high-throughput DNA sequence comparing adopts the high-throughput genotyping based on above Oxford Nanopore DNA sequencing.

- Because every SNP has biallelic alleles ALL-OR-NONE characteristics, based on one drug target gene SNP analysing, every drug response test can only have one of two results, i.e. positive result (+) or negative result (-), i.e., every drug therapeutic effect (efficacy) test or every drug side effect (risk) test can only have one of two results, i.e. positive result (+) or negative result (-), so, the mechanism of pharmacology and toxicology of any drugs need

never be guessed; the relationship between any drug target gene SNPs with any drug responses will be stable, and any drug target gene SNPs relating with any drug responses will surely be found. In SNP-pharmacogenomics clinical trials, if two double blind random separate groups' patients' drug target gene SNPs are the same; if the relationship between drug target gene SNPs and drug therapeutic effects are positive results (+), i.e. showing to have therapeutic effects, also if use these SNPs to define drug indication, this oncology drug chemotherapy efficacy can arrive higher than the 90% Effective Dose (ED90) level; if the relationship between drug target gene SNPs and drug side effects are negative results (-), i.e. showing to have no side effects, also if use these SNPs to define drug indication, this oncology drug chemotherapy risk can arrive lower than the 10% Lethal Dose (LD10) level.

- The classic oncology drug clinical trials must have placebo group, but the cancer patients in the placebo group will be equivalent to give up oncology drug treatments, so the placebo group cancer patients will surely die. But, because every SNP has biallelic alleles ALL-OR-NONE characteristics, in same one SNP clinical trial, toward same one therapeutic effect or same one side effect, all two of double-blind random separate group patient drug target gene SNPs will be the same. Therefore, only need set up two double-blind random separate groups of patients, and then treat same one cancer with two different combination chemotherapies including same oncology drugs separately in two different treating groups; in these SNP-pharmacogenomics clinical trials, the placebo group will surely be avoided. Like as this, even in the SNP clinical trial stage, also can rescue much many cancer patients' lives.

- This clinical project's success means that the cancer organ system limitation of oncology drug chemotherapy will be broken-through, meanwhile, the cancer patient population who can use specific one oncology drug will be expanded. Because based on SNP biallelic alleles ALL-OR-NONE characteristics, if the same Oncology Drug Therapeutic Effect Target Gene SNP is detected in different cancers, when using the same drug, any kinds of cancers having the same drug therapeutic effect target gene SNP will have same therapeutic effect; so, any kinds of cancers having the same drug therapeutic effect target gene SNP will be suitable for using the same drug to treat.

(*b*) the indication(s) to be studied -- **follow up Etoposide capsule DAILYMED Label**:

- **LABEL:** ETOPOSIDE capsule (https://dailymed.nlm.nih.gov/dailymed)
- Explore the relationship between single nucleotide polymorphisms and etoposide response and toxicity in patients with small cell lung cancer.

(*c*) the general approach to be followed in evaluating the drug:

- The usual approach to be followed in evaluating the drug (Etoposide)
- The study approach to be followed in evaluating the drug (Etoposide)

(*d*) the kinds of clinical trials to be conducted in the first year following the submission (if plans are not developed for the entire year, the sponsor should so indicate):

90 days -- Phase 2 **ANDA SNP** Oncology Clinical Trial (NCT01064466)

(*e*) the estimated number of patients to be given the drug in those studies;

- The usual approach group: 300 patients with Small Cell Lung Cancer (SCLC)
- The study approach group: 300 patients with Small Cell Lung Cancer (SCLC)

(*f*) any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug and related drugs.

- **Possible Side Effects of Etoposide** (Table Version Date: September 25, 2017)

The General Investigational plan [21 CFR 312.23(a)(3)]

The study patients of **Small Cell Lung Cancer (SCLC)** will treat with etoposide **without** pneumonectomy but with enough lung tissue biopsy and follow up the standard of care treatment with drug therapy in the Etoposide capsule DAILYMED Label Recommended Dose for **Small Cell Lung Cancer (SCLC)**.

- Criteria:

✧ Recruit 600 patients of **Small Cell Lung Cancer (SCLC)** who are suitable for enough lung tissue biopsy.
✧ The 600 **Small Cell Lung Cancer (SCLC)** patients are randomly separated to 2 groups via computer.
✧ **The usual approach randomization double-blinding active treatment concurrent control group:**
✓ Etoposide capsule 3 x 50 mg/day (Day 1 to Day 5 per week) (12 weeks)
✧ **The study approach randomization double-blinding active treatment concurrent control group:**
✓ China Import - Etoposide Capsule 3 x 50 mg/day (Day 1 to Day 5 per week) (12 weeks)
✧ Every lung cancer patient will receive lung tissue biopsy.
✧ Keep storing all lung biopsy tissues.
✧ Every lung cancer patient will receive peripheral blood-drawing.
✧ Keep storing all peripheral blood.
✧ All participating patients will need lung tissue biopsy test at least one time.
✧ All participating patients image test at least one time per month.
✧ All participating patients will need urine tests every week while they are taking oncology drugs.
✧ All participating patients will need blood tests every week while they are taking oncology drugs.
✧ Sequence precisely each target gene DNA whole chain in peripheral blood as follows: DNA Topoisomerase II.
✧ Sequence precisely each target gene DNA whole chain in peripheral blood as follows: CYP450 3A4.
✧ If any participating patients have serious side effects, they will be stopped the research.
✧ If any participating patients have no therapeutic effects, they will be stopped the research.

- Inclusion Criteria:

1. Clinical diagnosis of **Small Cell Lung Cancer (SCLC)**
2. Clinical lung tissue biopsy diagnosis of **Small Cell Lung Cancer (SCLC)**
3. Suitable for enough biopsy tissue of **Small Cell Lung Cancer (SCLC)**
4. Random and double blind
5. Measurable disease
6. Adequate organ functions
7. Adequate performance status
8. Age 22 years old and over
9. Receive blood-drawing
10. Sign an informed consent form

- Exclusion Criteria:

1. Pneumonectomy
2. Treatment with other anti-cancer therapies and cannot be stopped currently
3. Pregnancy
4. Breast-feeding
5. The patients with other serious inter-current illness or infectious diseases
6. Have more than one different kind of cancer at the same time
7. Serious Allergy Tendency
8. Clot and Bleed Tendency
9. Serious Risks or Serious Adverse Events of the drug product
10. The prohibition of the drug product
11. The participating patients have serious side effects
12. The participating patients have no therapeutic effects

The expected accrual populations:

- ✧ Recruit 600 patients of Small Cell Lung Cancer (SCLC) who are suitable for lung tissue biopsy.
- ✧ The 600 SCLC patients are randomly separated into 2 groups via computer.
- ✧ The usual approach group is 300 SCLC patients.
- ✧ The study approach group is 300 SCLC patients.
- ✧ Every SCLC patient will receive lung tissue biopsy.
- ✧ Keep storing all lung biopsy tissues of SCLC.
- ✧ Every SCLC patient will receive peripheral blood-drawing.
- ✧ Keep storing all peripheral blood.

The primary efficacy and safety endpoints:

- ➢ After lung tissue biopsy for each patient with Small Cell Lung Cancer (SCLC), through usual approach combined chemotherapy or study approach combined chemotherapy, in 90-days Phase 2 ANDA SNP Oncology Clinical Trial, there should not be cancer growth or cancer metastasis.
- ➢ If appear cancer growth or cancer metastasis, stop these patients' trial.
- ➢ If appear serious side effects or serious adverse reactions, stop these patients' trial.

The dose range:

- ✧ The usual approach randomization of double-blinding active treatment concurrent control group:
- ✓ Etoposide capsule - 3 x 50 mg/day (Day 1 to Day 5 per week) (12 weeks)

Drug Names	Targets in Peripheral Blood	Targets in Peripheral Blood
Etoposide Capsule	DNA Topoisomerase II	CYP450 3A4

- ✧ The study approach randomization of double-blinding active treatment concurrent control group:
- ✓ China Import Etoposide Capsule - 3 x 50 mg/day (Day 1 to Day 5 per week) (12 weeks)

Drug Names	Targets in Peripheral Blood	Targets in Peripheral Blood
China Import - Etoposide Capsule	DNA Topoisomerase II	CYP450 3A4

The analysis plans (statistical analysis plan):

- ✧ 600 SCLC patients will test peripheral blood DNA.
- ✓ Every SCLC patient will receive Topoisomerase II Gene SNPs test in peripheral blood DNA.
- ✓ Every SCLC patient will receive CYP450 3A4 Gene SNPs test in peripheral blood DNA.

- ✧ Sequence precisely every oncology drug target gene DNA whole chain.
- ✓ Sequence precisely Topoisomerase II gene DNA whole chain in peripheral blood.
- ✓ Sequence precisely CYP450 3A4 gene DNA whole chain in peripheral blood.
- ✧ Find every single nucleotide gene mutation site in every oncology drug target gene DNA whole chain.
- ✓ Find every single nucleotide gene mutation site in Topoisomerase II gene DNA whole chain.
- ✓ Find every single nucleotide gene mutation site in CYP450 3A4 gene DNA whole chain.
- ✧ If one single nucleotide gene mutation site appears ratio more than 1% in 600 SCLC patients, this is SNP.
- ✓ Calculate Topoisomerase II Gene SNPs in peripheral blood DNA in 600 SCLC patients.
- ✓ Calculate CYP450 3A4 Gene SNPs in peripheral blood DNA in 600 SCLC patients.

- ✧ If the peripheral blood samples of the usual approach group have the same oncology drug target gene SNP as the peripheral blood samples of the study approach group, the relationship between this oncology drug target gene SNP and this oncology drug efficacy can be confirmed, i.e. this oncology drug target gene SNP is related to this oncology drug efficacy.
- ✧ If the peripheral blood samples of the usual approach group have the same Topoisomerase II gene SNP as the peripheral blood samples of the study approach group, the relationship between this Topoisomerase II gene SNP and this ETOPOSIDE drug efficacy can be confirmed, i.e. this Topoisomerase II gene SNP is related to this ETOPOSIDE drug efficacy.

Target Gene SNP in Peripheral blood of Usual Approach Group of an SCLC patient	Target Gene SNP in Peripheral blood of Study Approach Group of an SCLC patient	Comparing Results
DNA Topoisomerase II Gene SNP	DNA Topoisomerase II Gene SNP	Same
This Topoisomerase II Gene SNP is related to the ETOPOSIDE drug efficacy.		

- ✧ If the peripheral blood samples of the usual approach group have the same oncology drug-target gene SNP as the peripheral blood samples of the study approach group, the relationship between this oncology drug target gene SNP and this oncology drug risk can be confirmed, i.e., this oncology drug target gene SNP is relating to this oncology drug risk.
- ✧ If the peripheral blood samples of the usual approach group have the same CYP450 3A4 gene SNP as the peripheral blood samples of the study approach group, the relationship between this CYP450 3A4 gene SNP and this ETOPOSIDE drug risk can be confirmed, i.e., this CYP450 3A4 gene SNP is relating to this ETOPOSIDE drug risk.

Target Gene SNP in Peripheral Blood of Usual Approach Group of an SCLC patient	Target Gene SNP in Peripheral Blood of Study Approach Group of an SCLC patient	Comparing Results
CYP450 3A4 Gene SNP	CYP450 3A4 Gene SNP	Same
This CYP450 3A4 Gene SNP is related to the ETOPOSIDE drug risk.		

The potential limitations of my proposed clinical trial:

The study patients will be treated the **Small Cell Lung Cancer (SCLC)** with etoposide <u>without</u> pneumonectomy. The ANDA SNP investigation will follow up the standard of care treatment with drug therapy in the Etoposide Capsule DAILYMED Label.

I (Han Xu, M.D., Ph.D. i.e., Sponsor i.e., Sponsor-Investigator) as IRB Chair of our IRB (IRB00009424) will only organize the IRB meeting but give up my voting power in the IRB determination, when I conduct my clinical investigation (NCT01064466).

Reference:

- ➢ Etoposide Capsule DAILYMED Label
- ➢ Possible Side Effects of Etoposide

Request to initiate and conduct ANDA SNP clinical trial NCT01064466:

I (Sponsor-Investigator) am planning to conduct an in vivo bioequivalence study in humans shall submit an "Investigational New Drug Application" (IND) (Etoposide IND 178172 Commercial), which the study (NCT01064466) involves a cytotoxic drug product (ETOPOSIDE capsule). Meanwhile, I am planning to conduct the bioequivalent study in humans using the drug product that contains an already approved, non-new chemical entity (Etoposide) shall submit the IND 178172, which the study (NCT01064466) is a single-dose study in patients with the maximum single in the labeling of the drug product (ETOPOSIDE capsule) that is the subject of an approved abbreviated new drug application (ANDA). The provisions of 21 CFR Part 50, 21 CFR Part 56, and 21 CFR Part 312 are applicable to my bioequivalence study (NCT01064466) in humans conducted under my IND 178172.

I (Han Xu, M.D., Ph.D. i.e., Sponsor i.e., Sponsor-Investigator) as IRB Chair of our IRB (IRB00009424) will organize the IRB meeting only but give up my voting power in the determination of IRB, when I conduct my clinical investigation (NCT01064466).

Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, Medical Director, IRB Chair, IORG Director

- NPI 1831468511 - Individual
  - Clinical Ethicist - (Code - 174V00000X)
  - Specialist Research Study - (Code - 1744R1102X)
  - Pharmacist, Pharmacist Clinician (PhC) / Clinical Pharmacy Specialist (Code - 1835P0018X)
- **Certificate of Fellow of Academy of Physicians in Clinical Research (FAPCR)**
  Academy of Physicians in Clinical Research (APCR)
  - Principal Investigator (PI) in clinical trials
  - Medical Director of Clinical Research Site
- **Medicine Invention Design Incorporation (MIDI) (IORG0007849)**
  - IORG Director (IORG0007849)
- **Medicine Invention Design Incorporation (MIDI) IRB #1 (IRB00009424)**
  - IRB Chair (IRB00009424)
- **Federal-wide Assurance (FWA) for the Protection of Human Subjects (FWA00015357)**
  - Human Subjects Administrator (FWA00015357)
- **FDA Wholesale Drug Distributor (Maryland License Number: D11379922)**
  - Medical Director (D11379922)
- NPI 1023387701 - Organization
  - Multi-Specialty Group (Code - 193200000X)
  - Research Clinic/Center - (Code - 261QR1100X)
  - Clinical Medical Laboratory - (Code - 291U00000X)
  - **Health Maintenance Organization - (Code - 302R00000X)**
  - Managed Care Organization Pharmacy (Code - 3336M0003X)
  - Mail Order Pharmacy - (Code - 3336M0002X)
  - FDA Wholesale Drug Distributor (Maryland License Number: D11379922)
  - Distribute human drug products under own private label (FDA NDC Labeler Code - 69891)
  - FDA Establishment Identifier (FEI Number - 300363713)
- My IND has been granted. My pre-assigned number is IND 178172.
  - Sponsor: HAN XU
  - Sponsor: Medicine Invention Design Incorporation
- **ClinicalTrials.gov ID: NCT01064466** under **42 CFR Part 11**
  - Responsible Party: **Sponsor-Investigator:** Han Xu, M.D., Ph.D., FAPCR
  - Study Principal Investigator [**Principal Investigator (PI)**]: Han Xu, M.D., Ph.D., FAPCR
  - Study Director (**Medical Director**): Han Xu, M.D., Ph.D., FAPCR
  - Study Chair (**IRB Chair**): Han Xu, M.D., Ph.D., FAPCR

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