Cover Page

Release Date: August 25, 2025

ClinicalTrials.gov ID: NCT07145333

Unique Protocol ID: IND 178174 Commercial

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

Official Title: Explore the Relationship Between Single Nucleotide Polymorphisms and Topotecan 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: HHS, IRB]
IORG0007849 [Registry ID: HHS, IORG]
IND178174 [Registry ID: FDA, IND]

Contents

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.

Study Protocol [21 CFR 312.23(a)(6)(iii)] for ANDA SNP Clinical Trial

ANDA SNP - NCT07145333 Clinical Trial is a **Sponsor-Investigator** Clinical Study.

Han Xu, **Sponsor-Investigator** will be able to initiate and conduct the Study Protocol [21 CFR 312.23(a)(6)(iii)].

- My IND has been granted. My pre-assigned number is IND 178174.
  - Sponsor: HAN XU
  - Sponsor: Medicine Invention Design Incorporation
- **ClinicalTrials.gov ID: NCT07145333** 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

The protocol is to contain the following, with the specific elements and detail of the protocol reflecting the above distinctions depending on the Phase 2 of the ANDA SNP study:

(a) A statement of the objectives and purpose of the study.

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

- Correlate Topoisomerase I Gene Single Nucleotide Polymorphisms (SNPs) to Therapeutic Effects of Using Topotecan to Treat Small Cell Lung Cancer (SCLC), based on precisely sequencing drug target gene via peripheral blood WBC DNA.
- Correlate CYP450 3A4 Gene Single Nucleotide Polymorphisms (SNPs) to Side Effects of Using Topotecan to Treat Small Cell Lung Cancer (SCLC), based on precisely sequencing drug target gene via WBC DNA.

(b) The name and address and a statement of the qualifications (curriculum vitae or **other statement of qualifications**) of sponsor-investigator or each investigator, and the name of each Principal Investigator or sub-investigator (e.g., research fellow, resident) working under the supervision of the sponsor-investigator; the name and address of the research facilities to be used; and the name and address of each reviewing Institutional Review Board.

The name of sponsor-investigator: Han Xu, M.D., Ph.D., Sponsor-Investigator, IRB Chair, Medical Director
The address of sponsor-investigator: 5545 Burnside Drive, Online Site, Rockville, Maryland, 20853

The name of the IRB: IRB00009424 -- Medicine Invention Design Incorporation (MIDI) IRB #1
The Address of the IRB: 5545 Burnside Drive, Online Site, Rockville, Maryland, 20853

The name of the research facility: IORG0007849 -- Medicine Invention Design Incorporation (MIDI)
The address of the research facility: 5545 Burnside Drive, Online Site, Rockville, Maryland, 20853

The statement of the qualifications of Sponsor-Investigator:

- 2020 - Active Member, Fellow of the APCR (FAPCR), Academy of Physicians in Clinical Research (APCR) - APCR Membership Eligibility - Physician Investigator
  - Certificate of Fellow of Academy of Physicians in Clinical Research (FAPCR)
  - Academy of Physicians in Clinical Research (APCR)
    - **PI (Principal Investigator) in clinical trials**
    - **Medical Director of Clinical Research Site**
- 2025 - My IND has been granted. My pre-assigned number is IND 178174.
  - Sponsor: HAN XU
  - Sponsor: Medicine Invention Design Incorporation
- 2025 - **ClinicalTrials.gov ID: NCT07145333** under **42 CFR Part 11**
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  - Study Director (**Medical Director**): Han Xu, M.D., Ph.D., FAPCR
  - Study Chair (**IRB Chair**): Han Xu, M.D., Ph.D., FAPCR

(c) The criteria for patient selection and for exclusion of patients and an estimate of the number of patients to be studied.

- Criteria:
  - Select 600 Small-Cell Lung Cancer (SCLC) Patients who are suitable for lung tissue biopsy
  - Duration at least 90 days
  - The usual approach group - Recruit 300 double blind random group separated SCLC patients currently used the Chemotherapy on Topotecan CAPSULE after lung tissue biopsy, as the usual approach group.
  - The study approach group - Recruit 300 double blind random group separated SCLC patients currently used the Chemotherapy on **China Import** Topotecan CAPSULE after lung tissue biopsy, as the study approach group.
  - 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:
  - Clinical diagnosis of small cell lung cancer
  - Clinical biopsy diagnosis of small cell lung cancer
  - Suitable for lung tissue biopsy
  - Random and double blind
  - Measurable disease
  - Adequate organ functions
  - Adequate performance status
  - Age 22 years old and over
  - Sign an informed consent form.
  - Receive blood-drawing.

- Exclusion Criteria:
  - Pneumonectomy
  - Treatment with other anti-cancer therapies and cannot be stopped currently
  - Pregnancy
  - Breast-feeding
  - The patients with other serious inter-current illness or infectious diseases
  - Have more than one different kind of cancer in the same time
  - Serious Allergy Tendency
  - Serious Bleed Tendency
  - Serious Risks or Serious Adverse Events of the drug product
  - The prohibition of the drug product
  - The participating patients have serious side effects
  - The participating patients have no therapeutic effects

(d) A description of the design of the study, including the kind of control group to be used, if any, and a description of methods to be used to minimize bias on the part of subjects, investigators, and analysts.

The usual approach group, after lung tissue biopsy, 300 double blind random group separated SCLC patients currently using the Chemotherapy on TOPOTECAN CAPSULE, based on precisely sequencing drug targets' genes, will try to do the following:

- Correlate Topoisomerase I Gene Single Nucleotide Polymorphisms (SNPs) to Therapeutic Effects of Using TOPOTECAN to Treat Small Cell Lung Cancer (SCLC), via Testing Peripheral Blood DNA.
- Correlate CYP450 3A4 Gene Single Nucleotide Polymorphisms (SNPs) to Side Effects of Using TOPOTECAN to Treat Small Cell Lung Cancer (SCLC), via Testing Peripheral Blood DNA.

The study approach group, after lung tissue biopsy, 300 double blind random group separated SCLC patients currently using the Chemotherapy on **China Import** TOPOTECAN CAPSULE, based on precisely sequencing drug targets' genes, will try to do the following:

- Correlate Topoisomerase I Gene Single Nucleotide Polymorphisms (SNPs) to Therapeutic Effects of Using TOPOTECAN to Treat Small Cell Lung Cancer (SCLC), via Testing Peripheral Blood DNA.
- Correlate CYP450 3A4 Gene Single Nucleotide Polymorphisms (SNPs) to Side Effects of Using TOPOTECAN to Treat Small Cell Lung Cancer (SCLC), via Testing Peripheral Blood DNA.

The detailed methods:

1) Detect each drug target whole gene precision sequence of everyone patient for all 600-recruited double-blind SCLC patients.

- Oxford Nanopore Technologies Ltd - 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.
- DNA Sequencing
- Prepare
- ✓ Streamlined library prep in as little as 10 minutes
- ✓ PCR-free library prep using 400 ng DNA
- ✓ PCR option for very low input amounts
- ✓ Multiplexing options for more cost-effective analysis
- Sequence
- ✓ Real-time sequencing on MinION, GridION or PromethION
- Analyses
- ✓ Real-time analysis with on device or local infrastructure base-calling
- ✓ Detect DNA modifications using open-source tools

2) Mutually compare everyone patient drug target whole gene precision sequence for total 600-recruited double-blind SCLC patients.
3) Calculate each drug target gene SNP in all 600-recruited double-blind SCLC patients.
4) Correlate everyone patient drug target gene SNP to everyone patient drug efficacy.
5) Correlate everyone patient drug target gene SNP to everyone patient drug safety.
6) Mutually compare the usual approach group SNPs (300 double blind random group separated SCLC patients) with the study approach group SNPs (300 double blind random group separated SCLC patients).
7) Confirm the relationship between drug target gene SNPs and drug efficacy.

(e) The method for determining the dose(s) to be administered, the planned maximum dosage, and the duration of individual patient exposure to the drug.

The method for determining the dose(s) to be administered:

- See Topotecan Capsule USP Label

The planned maximum dosage(s):

Topotecan Capsule -- 3 x 50 mg/day (Day 1 to Day 5 per week) (12 weeks)

The duration of individual patient exposure to the drug(s):
Topotecan Capsule -- (Day 1 to Day 5 per week) (12 weeks) = 60 days
The total duration of Phase 2 clinical trial = 90 days

(f) A description of the observations and measurements to be made to fulfill the objectives of the study.

- Sequence precisely each target gene DNA whole chain in peripheral blood as follows:
  DNA Topoisomerase I.

- Correlate Topoisomerase I Gene Single Nucleotide Polymorphisms (SNPs) to Therapeutic Effects of Using Topotecan to Treat SCLC, based on precisely sequencing drug target gene via WBC DNA.
- Sequence precisely each target gene DNA whole chain in peripheral blood as follows: CYP450 3A4.
- Correlate CYP450 3A4 Gene Single Nucleotide Polymorphisms (SNPs) to Side Effects of Using Topotecan to Treat SCLC, based-on precisely sequencing drug target gene via WBC DNA.
- Oxford Nanopore Technologies Ltd - 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.
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- ✓ Detect DNA modifications using open-source tools

(g) A description of clinical procedures, laboratory tests, or other measures to be taken to monitor the effects of the drug in human subjects and to minimize risk.

The clinical procedures:

- ✧ 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 cancer tissues.
- ✧ Every SCLC patient will receive peripheral blood-drawing.
- ✧ Keep storing all peripheral blood.
- ✧ Every SCLC patient will receive testing for each Target Gene SNP in peripheral blood DNA as follows: DNA Topoisomerase I.
- ✧ Every SCLC patient will receive testing for each Target Gene SNP in peripheral blood DNA as follows: CYP450 3A4.
- ✧ The usual approach group (300 SCLC patients) for everyone:
- ✓ Topotecan Capsule - 3 x 50 mg/day (Day 1 to Day 5 per week) (12 weeks)
- ✓ Sequence precisely each target gene DNA whole chain in peripheral blood as follows: DNA Topoisomerase I.
- ✓ Correlate Topoisomerase I Gene Single Nucleotide Polymorphisms (SNPs) to Therapeutic Effects of Using TOPOTECAN to Treat Small Cell Lung Cancer (SCLC), via Testing Peripheral Blood DNA.
- ✓ Sequence precisely each target gene DNA whole chain in peripheral blood as follows: CYP450 3A4.
- ✓ Correlate CYP450 3A4 Gene Single Nucleotide Polymorphisms (SNPs) to Side Effects of Using TOPOTECAN to Treat Small Cell Lung Cancer (SCLC), via Testing Peripheral Blood DNA.
- ✧ The study approach group (300 SCLC patients) for everyone:
- ✓ **China Import** Topotecan Capsule - 3 x 50 mg/day (Day 1 to Day 5 per week) (12 weeks)
- ✓ Sequence precisely each target gene DNA whole chain in peripheral blood as follows: DNA Topoisomerase I.

- ✓ Correlate Topoisomerase I Gene Single Nucleotide Polymorphisms (SNPs) to Therapeutic Effects of Using TOPOTECAN to Treat Small Cell Lung Cancer (SCLC), via Testing Peripheral Blood DNA.
- ✓ Sequence precisely each target gene DNA whole chain in peripheral blood as follows: CYP450 3A4.
- ✓ Correlate CYP450 3A4 Gene Single Nucleotide Polymorphisms (SNPs) to Side Effects of Using TOPOTECAN to Treat Small Cell Lung Cancer (SCLC), via Testing Peripheral Blood DNA.
- ✧ Every SCLC patient will receive image test one time per month.
- ✧ Every SCLC patient will receive blood test one time per week.
- ✧ Every SCLC patient will receive urine test one time per week.
- ✧ Every SCLC patient will receive ECG test one time per week.
- ✧ The clinical study endpoint is SCLC metastasis or growth.
- ✧ The drug efficacy standard is to avoid SCLC metastasis or growth in 90 days.
- ✧ The drug risk standard is occurring leucopenia.
- ✧ Mutually compare the usual approach group SNPs (300 double-blind random group separated SCLC patients) with the study approach group SNPs (300 double-blind random group separated SCLC patients).
- ✧ Confirm the relationship between drug target gene SNPs and drug efficacy.
- ✧ If the peripheral blood samples of the usual approach group have the same Topoisomerase I Gene SNP as the peripheral blood samples of the study approach group, the relationship between the TOPOTECAN drug target gene SNP and the TOPOTECAN drug efficacy can be confirmed, i.e. this Topoisomerase I Gene SNP is the TOPOTECAN drug target gene SNP relating to the TOPOTECAN drug efficacy.
- ✧ Confirm the relationship between drug target gene SNPs and 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 the TOPOTECAN drug target gene SNP and the TOPOTECAN drug risk can be confirmed, i.e. this CYP450 3A4 Gene SNP is the TOPOTECAN drug target gene SNP relating to the TOPOTECAN drug risk.

The laboratory tests:

- ✧ Recruit 600 patients of Small Cell Lung Cancer (SCLC) who are suitable for lung tissue biopsy.
- ✧ Every SCLC patient will receive lung tissue biopsy.
- ✧ Keep storing all cancer tissues.
- ✧ Every SCLC patient will receive peripheral blood-drawing.
- ✧ Keep storing all peripheral blood.
- ✧ Detect every drug target's whole gene precision sequence of every patient for all 600 SCLC patients.
- ➢ Oxford Nanopore Technologies Ltd - 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.
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- ✓ Detect DNA modifications using open-source tools.

- ✧ Every SCLC patient will receive sequencing each target gene DNA whole chain in peripheral blood as follows: DNA Topoisomerase I.
- ✧ Every SCLC patient will receive sequencing each target gene DNA whole chain in peripheral blood as follows: CYP450 3A4.
- ✧ Mutually compare every drug target whole gene precision sequence of every patient for total 600 SCLC patients.
- ✧ Obtain every-one Target Gene SNP for every SCLC patient in Peripheral Blood DNA as follows: DNA Topoisomerase I.
- ✧ Obtain every-one Target Gene SNP for every SCLC patient in Peripheral Blood DNA as follows: CYP450 3A4.
- ✧ Every SCLC patient will receive image test one time per month.
- ✧ Every SCLC patient will receive blood test one time per week.
- ✧ Every SCLC patient will receive urine test one time per week.
- ✧ Every SCLC patient will receive ECG test one time per week.

The measures to be taken to monitor the effects of the drug in human subjects:

- ✧ The clinical study endpoint is SCLC metastasis or growth.
- ✧ The drug efficacy standard is to avoid SCLC metastasis or growth in 90 days.
- ✧ Every SCLC patient will receive image test one time per month.

The measures to be taken to minimize the risks of the drug in human subjects:

- ✧ Every SCLC patient will receive image test one time per month.
- ✧ Every SCLC patient will receive blood test one time per week.
- ✧ Every SCLC patient will receive urine test one time per week.
- ✧ Every SCLC patient will receive ECG test one time per week.

- ✧ Hypocytharemia -- Erythropoietin (EPO)
- ✧ Neutropenia -- Granulopoietin - Granulocyte-Colony Stimulating Factor (G-CSF or GCSF)
- ✧ Lymphopenia -- Interleukin-2 (IL-2)
- ✧ Thrombocytopenia -- Interleukin-11 (IL-11)
- ✧ Emesis -- Alosetron, Dolasetron, Granisetron, Ondansetron, Palonosetron

The study patients of SCLC follow up the standard of care treatment with drug therapy in the Topotecan Capsule USP Label

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.
In order to avoid treating SCLC with platium, I designed the ANDA SNP Protocol NCT07145333.

21 CFR§56.102 (i)
Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

The IRB00009424 must let all subjects sign a written consent form and will let the research NCT07145333 present no more than minimal risk of harm to subjects as well as will let the research NCT07145333 involve no procedures for outside the written consent document context.

21 CFR§56.111 (a) (1)
Risks to subjects are minimized: (i) By using procedures which are consistent with sound research design, and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

The study patients of SCLC follow up the standard of care treatment with drug therapy in the Topotecan Capsule USP Label

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If any participating patients have no therapeutic effects, they will be stopped the research.
In order to avoid treating SCLC with platium, I designed the ANDA SNP Protocol NCT07145333.

I (Sponsor-Investigator) am planning to conduct an in vivo bioequivalence study in humans shall submit an "Investigational New Drug Application" (IND) (Topotecan IND 178174 Commercial), which the study (NCT07145333) involves a cytotoxic drug product (Topotecan 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 (Topotecan) shall submit the IND 178174, which the study (NCT07145333) is a single-dose study in patients with the maximum single in the labeling of the drug product (Topotecan 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 (NCT07145333) in humans conducted under my IND 178174.

21 CFR 56.102(g)
Institutional Review Board (IRB) means any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects.

21 CFR 56.102(m)
IRB approval means the determination of the IRB that the clinical investigation has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

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 determination of IRB, when I conduct my clinical investigation (NCT07145333).

21CFR§50.3 (f)
Sponsor-investigator means an individual who both initiates and actually conducts, alone or with others, a clinical investigation, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include any person other than an individual, e.g., corporation or agency.

- **ClinicalTrials.gov ID: NCT07145333** 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

21 CFR 312.23(a)(1)(v)
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Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, Medical Director, IRB Chair, IORG Director
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