# Cover Page

**Release Date:** December 27, 2023

**ClinicalTrials.gov ID:** NCT05987956

**Unique Protocol ID:** IND 168453 to be IND EXEMPT

**Brief Title:** Pharmacogenomics IND EXEMPT SNP Clinical Study - Alectinib and Single Nucleotide Polymorphisms (Drugs-SNPs)

**Official Title:** Explore the Relationship Between Single Nucleotide Polymorphisms and Alectinib Response and Toxicity in Patients with Non-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]
IND 168453 [Registry ID: FDA, IND EXEMPT]

# Contents



I think that my clinical study (NCT05987956) meets all of the requirements for exemption from the IND regulations [21 CFR 312.2(b)] and, therefore, an IND is not required to conduct my clinical investigation. The IND regulations [21 CFR 312.2(b)] state that my clinical investigation of oncology drug product (Alectinib Capsule) that is lawfully marketed in the United States is exempt from the requirements for an IND, also is exempt from the requirements of this part (i.e., 21 CFR Part 312); i.e., my clinical investigation is exempt from all requirements in whole 21 CFR Part 312. My clinical investigation (NCT05987956) is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for my oncology drug (Alectinib Capsule). My investigation is not intended to support a significant change in the advertising for a prescription drug product; does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product; is conducted in compliance with the requirements for institutional review (21 CFR Part 56) and informed consent (21 CFR Part 50); is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective for the purposes for which it is under investigation, nor may it be commercially distributed or sold. 21 CFR 312.2(b)(5) exempts from the IND requirements my clinical investigation that involves use of a placebo, and investigation does not otherwise require submission of an IND. My IND 168453 should be IND EXEMPT. The IND EXEMPT SNP clinical trial NCT05987956 will explore the relationship between single nucleotide polymorphisms and alectinib response and toxicity in patients with non-small cell lung cancer. I request to initiate and conduct IND EXEMPT SNP clinical trial NCT05987956 based on IND 168453 to be IND EXEMPT.

**21 CFR 312.53(c)(1)(vi)(*d*)**
**21 CFR 312.2(b)(1)(iv)**

**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:
NDC: 50242-130-01 (ALECENSA - alectinib hydrochloride capsule) (NDA208434)
NDC: 50242-130-86 (ALECENSA - alectinib hydrochloride capsule) (NDA208434)

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

The structural formula of the drug:
**LABEL:** ALECENSA - alectinib hydrochloride capsule (https://dailymed.nlm.nih.gov)

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

Usual Approach Group
NDC: 50242-130-01 (ALECENSA - Alectinib Capsule) (NDA208434) -- 600 mg orally twice daily.

Study Approach Group
NDC: 50242-130-86 (ALECENSA - Alectinib Capsule) (NDA208434) -- 600 mg orally twice 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 alectinib response and toxicity in patients with non-small cell lung cancer.

The planned duration of my proposed clinical investigation:

90 days -- Phase 2 **IND EXEMPT SNP** Oncology Clinical Investigation **NCT05987956**

(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:** ALECENSA - alectinib hydrochloride capsule (https://dailymed.nlm.nih.gov)

(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 (ALECENSA - alectinib hydrochloride capsule) 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 **IND EXEMPT SNP** Oncology Clinical Investigation **NCT05987956**

*(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 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 Alectinib Capsule DAILYMED Label**:

- **LABEL:** ALECENSA - alectinib hydrochloride capsule (**DAILYMED:** https://dailymed.nlm.nih.gov)
- Explore the relationship between single nucleotide polymorphisms and alectinib response and toxicity in patients with non-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 (Alectinib)
- The study approach to be followed in evaluating the drug (Alectinib)

(*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 **IND EXEMPT SNP** Oncology Clinical Trial **NCT05987956**

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

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

(*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.

**21 CFR 312.2(b)(1)(iii)**
The investigation does **not** involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product; …

- **LABEL:** ALECENSA - alectinib hydrochloride capsule (**DailyMed:** https://dailymed.nlm.nih.gov)

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

The study patients of **Non-Small Cell Lung Cancer (NSCLC)** will treat with alectinib **without** pneumonectomy but with enough peripheral blood mononuclear cells and follow up the standard of care treatment with drug therapy in the Alectinib Capsule DAILYMED Label i.e., Recommended Dose for **Non-Small Cell Lung Cancer (NSCLC)** i.e., Alectinib Capsule, DAILYMED as first line treatment in patients with non-small cell lung cancer.

- Criteria:

✧ Recruit 600 patients of **Non-Small Cell Lung Cancer (NSCLC)** who are suitable for drawing peripheral blood.
✧ The 600 **Non-Small Cell Lung Cancer (NSCLC)** patients are randomly separated into 2 groups via computer.
✧ **The usual approach randomization double-blinding active treatment concurrent control group:**
✓ ALECENSA - alectinib hydrochloride capsule -- 600 mg orally twice daily (12 weeks)
✧ **The study approach randomization double-blinding active treatment concurrent control group:**
✓ ALECENSA - alectinib hydrochloride capsule -- 600 mg orally twice daily (12 weeks)
✧ Every lung cancer patient will receive draw peripheral blood.
✧ Keep storing all peripheral blood mononuclear cells.
✧ Every lung cancer patient will receive peripheral blood-drawing.
✧ Keep storing all peripheral blood.
✧ All participating patients will need a blood-drawing 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 like as following: ALK.
✧ Sequence precisely each target gene DNA whole chain in peripheral blood like as following: CYP3A4.
✧ 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 **Non-Small Cell Lung Cancer (NSCLC)**
2. Clinical biopsy diagnosis of **Non-Small Cell Lung Cancer (NSCLC)**
3. Suitable for draw peripheral blood
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 the therapies 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. Serious 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 Non-Small Cell Lung Cancer (NSCLC) who are suitable blood-drawing.
- ✧ The 600 NSCLC patients are randomly separated into 2 groups via computer.
- ✧ The usual approach group is 300 NSCLC patients.
- ✧ The study approach group is 300 NSCLC patients.
- ✧ Every NSCLC patient will receive peripheral blood-drawing.
- ✧ Keep storing all peripheral blood.

**The primary efficacy and safety endpoints:**

- After peripheral blood-drawing for each patient with **Non-Small Cell Lung Cancer (NSCLC)**, through usual approach chemotherapy or study approach chemotherapy, in 90-days Phase 2 IND EXEMPT 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 statistical table):**

- ✧ The usual approach randomization double-blinding active treatment concurrent control group:
- ✓ ALECENSA - alectinib hydrochloride capsule -- 600 mg orally twice daily (12 weeks)

| Drug Names | Targets in Peripheral Blood | Targets in Peripheral Blood |
|---|---|---|
| Alectinib Capsule | ALK | CYP3A4 |

- ✧ The study approach randomization double-blinding active treatment concurrent control group:
- ✓ ALECENSA - alectinib hydrochloride capsule -- 600 mg orally twice daily (12 weeks)

| Drug Names | Targets in Peripheral Blood | Targets in Peripheral Blood |
|---|---|---|
| Alectinib Capsule | ALK | CYP3A4 |

**The analysis plans (The statistical analysis plan):**

- ✧ 600 NSCLC patients will test peripheral blood DNA.
- ✓ Every NSCLC patient will receive testing for ALK Gene SNPs in peripheral blood DNA.
- ✧ 600 NSCLC patients will test peripheral blood DNA.
- ✓ Every NSCLC patient will receive testing CYP3A4 Gene SNPs in peripheral blood DNA.

- ✧ Sequence precisely every oncology drug target gene DNA whole chain.
- ✓ Sequence precisely ALK gene DNA whole chain in peripheral blood……

- ✓ Sequence precisely CYP3A4 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 ALK gene DNA whole chain.
- ✓ Find every single nucleotide gene mutation site in CYP3A4 gene DNA whole chain.
- ✧ If one single nucleotide gene mutation site appears ratio more than 1% in 600 NSCLC patients, this is SNP.
- ✓ Calculate ALK Gene SNPs in peripheral blood DNA in 600 NSCLC patients.
- ✓ Calculate CYP3A4 Gene SNPs in peripheral blood DNA in 600 NSCLC 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 relating to this oncology drug efficacy.
- ✧ If peripheral blood samples of the usual approach group have the same ALK gene SNP as peripheral blood samples of the study approach group, the relationship between this ALK gene SNP and this Alectinib oncology drug efficacy can be confirmed, i.e., this ALK gene SNP is relating to this Alectinib oncology drug efficacy.

| Target Gene SNP in Peripheral Blood of Usual Approach Group of an NSCLC patient | Target Gene SNP in Peripheral Blood of Study Approach Group of an NSCLC patient | Comparing Results |
|---|---|---|
| ALK Gene SNP | ALK Gene SNP | Same |
| This ALK Gene SNP is related to the Alectinib 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 CYP3A4 gene SNP as the peripheral blood samples of the study approach group, the relationship between this CYP3A4 gene SNP and this Alectinib drug risk can be confirmed, i.e., this CYP3A4 gene SNP is relating to this Alectinib drug risk.

| Target Gene SNP in Peripheral Blood of Usual Approach Group of an NSCLC patient | Target Gene SNP in Peripheral Blood of Study Approach Group of an NSCLC patient | Comparing Results |
|---|---|---|
| CYP3A4 gene SNP | CYP3A4 gene SNP | Same |
| This CYP3A4 Gene SNP is related to the Alectinib drug risk. | | |

**The potential limitations of my proposed clinical trial:**

The study patients will be treated the **Non-Small Cell Lung Cancer (NSCLC)** with Alectinib without pneumonectomy. The IND EXEMPT SNP investigation will follow up the standard of care treatment with drug therapy in the ALECENSA - alectinib hydrochloride 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 **(NCT05987956)**.

**Reference:**


- **LABEL:** ALECENSA - alectinib hydrochloride capsule (**DAILYMED:** https://dailymed.nlm.nih.gov)


**Request FDA approve IND 168453 to be IND EXEMPT SNP clinical trial NCT05987956:**

My clinical study (NCT05987956) meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct my clinical investigation; i.e., my clinical investigation of oncology drug product (Alectinib Capsule) that is lawfully marketed in the United States is exempt from the requirements for an IND, also is exempt from the requirements of this part (i.e., 21 CFR Part 312); i.e., my clinical investigation is exempt from the requirements of investigator in whole 21 CFR Part 312; meanwhile, my investigation does **not** involve **FORM FDA 1571 Item 14,** e.g., ***Expanded Access Use, 21 CFR 312.300*****,** i.e., ***21 CFR Part 312 - Subpart I - Expanded Access to Investigational Drugs for Treatment Use***; so, my clinical investigation is exempt from the requirements of 21 CFR Part 312 for treatment and investigator. So, I am a qualified investigator for my IND EXEMPT SNP oncology drug clinical investigation. In my APCR documents, Han Xu, M.D., Ph.D., FAPCR had been defined as **PI (Principal Investigator)** in clinical trials. In my document **ClinicalTrials.gov ID:** NCT05987956, I (Han Xu, M.D., Ph.D., FAPCR) am defined as Responsible Party (Sponsor-Investigator) and Study Principal Investigator [Principal Investigator (PI)]. So, Han Xu, M.D., Ph.D. must be the sponsor-investigator (S-I) of my clinical trial. So, I (Han Xu, Sponsor-Investigator) can both initiate and conduct, alone or with others, my clinical investigation (NCT05987956).

My clinical investigation (NCT05987956) is not intended to be reported to FDA as a well-controlled study in support of a new indication for use, nor intended to be used to support any other significant change in the labeling for my oncology drug (Alectinib Capsule). My investigation is not intended to support a significant change in the advertising for a prescription drug product; does not involve a change in route of administration, dosage level, or patient population, or other factor that significantly increases the risks (or decreases the acceptability of risks) associated with use of the drug product; is conducted in compliance with the requirements for institutional review (21 CFR Part 56) and informed consent (21 CFR Part 50); is conducted in compliance with the requirements of 21 CFR 312.7, i.e., the drug may not be represented as safe or effective for the purposes for which it is under investigation, nor may it be commercially distributed or sold. 21 CFR 312.2(b)(5) exempts from the IND requirements my clinical investigation that involves use of a placebo, and investigation does not otherwise require submission of an IND. My IND 168453 should be IND EXEMPT. The IND EXEMPT SNP clinical trial **NCT05987956** will explore the relationship between single nucleotide polymorphisms and alectinib response and toxicity in patients with non-small cell lung cancer. I am requesting FDA approve my **IND 168453 to be IND EXEMPT** SNP clinical trial **NCT05987956** via this pre-IND meeting with **Written response only** -- WRO by email.

**21 CFR 312.2(b)(1)(iv)**
The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50.

**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 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.

According to 21 CFR 56.102(g), Institutional Review Board (IRB) (IRB00009424) can approve the initiation of, and can conduct periodic review of, biomedical research involving human subjects (NCT05987956).

**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.

According to 21 CFR 56.102(m), IRB approval means the determination of our IRB (IRB00009424) that my clinical investigation (NCT05987956) has been reviewed and may be conducted at our institution (Medicine Invention Design Incorporation) within the constraints set forth by our IRB (IRB00009424) and by other institutional and Federal requirements.

**21 CFR 56.107(e)**
No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

According to 21 CFR 56.107(e), I (Han Xu, M.D., Ph.D., FAPCR, 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 (NCT05987956).

The investigation (**NCT05987956**) will be conducted in compliance with the requirements for **21 CFR Part 56** like as following:

**21 CFR § 56.102 (k)**
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., it does not include a corporation or agency. The obligations of a sponsor-investigator under this part include both those of a sponsor and those of an investigator.

I (Han Xu, **sponsor-investigator**) will actually conduct, with online referral clinical investigators, the clinical investigation (NCT05987956), i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject.

Our investigation (**NCT05987956**) will be conducted in compliance with the requirements for **21 CFR Part 50** like as following:

**21 CFR § 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.

I (Han Xu, **sponsor-investigator**) will actually conduct, with online referral clinical investigators, the clinical investigation (NCT05987956), i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject.

**Han Xu, M.D., Ph.D., FAPCR, Sponsor-Investigator, Medical Director, IRB Chair, IORG Director**
**NPI 1831468511 - Individual**
Clinical Ethicist - (Code - 174V00000X)
**ClinicalTrials.gov ID: NCT05987956**
Responsible Party: **Sponsor-Investigator**
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