# Cover Page

**Release Date:** June 23, 2025

**ClinicalTrials.gov ID:** NCT06062810

**Unique Protocol ID:** ANDA 220176

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

**Official Title:** Explore the Relationship Between Single Nucleotide Polymorphisms and Raloxifene Response and Toxicity in Patients With Breast Cancer LCIS.

**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]
ANDA 220176 [Registry ID: FDA, ANDA]

# Contents



## 21 CFR §312.23 (a)(3)

(3) Introductory statement and general investigation 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: 71209-082-01 (RALOXIFENE HYDROCHLORIDE tablet, coated) (ANDA211324) (Generic-1)
NDC: 72241-010-22 (RALOXIFENE HYDROCHLORIDE tablet, coated) (ANDA211324) (Generic-2)

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

The structural formula of the drug:
**LABEL:** RALOXIFENE HYDROCHLORIDE tablet, coated (https://dailymed.nlm.nih.gov) (Generic-1)
**LABEL:** RALOXIFENE HYDROCHLORIDE tablet, coated (https://dailymed.nlm.nih.gov) (Generic-2)

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

Usual Approach Group
NDC: 71209-082-01 (RALOXIFENE HYDROCHLORIDE tablet, coated) (ANDA211324) -- 60 mg orally daily.

Study Approach Group
NDC: 72241-010-22 (RALOXIFENE HYDROCHLORIDE tablet, coated) (ANDA211324) -- 60 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 raloxifene response and toxicity in patients with breast cancer showing lobular carcinoma in situ (LCIS) (BC-LCIS).

The planned duration of my proposed clinical investigation:

90 days -- Phase 2 **ANDA SNP** Oncology Clinical Investigation **NCT06062810**

(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:** RALOXIFENE HYDROCHLORIDE tablet, coated (https://dailymed.nlm.nih.gov) (Generic-1)
**LABEL:** RALOXIFENE HYDROCHLORIDE tablet, coated (https://dailymed.nlm.nih.gov) (Generic-2)

(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 (RALOXIFENE HYDROCHLORIDE tablet, coated) 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 **NCT06062810**

*(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 Raloxifene Tablet DAILYMED Label**:

- **LABEL:** RALOXIFENE HYDROCHLORIDE tablet, coated (**DAILYMED:** https://dailymed.nlm.nih.gov) (G-1)
- **LABEL:** RALOXIFENE HYDROCHLORIDE tablet, coated (**DAILYMED:** https://dailymed.nlm.nih.gov) (G-2)
- Explore the relationship between single nucleotide polymorphisms and raloxifene response and toxicity in patients with breast cancer showing lobular carcinoma in situ (LCIS) (BC-LCIS).

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

- The usual approach to be followed in evaluating the drug (Raloxifene) (Generic-1)
- The study approach to be followed in evaluating the drug (Raloxifene) (Generic-1)

(*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 indicate so):

90 days -- Phase 2 **ANDA SNP** Oncology Clinical Trial **NCT06062810**

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

- The usual approach group: 300 patients with Breast Cancer LCIS (BC-LCIS)
- The study approach group: 300 patients with Breast Cancer LCIS (BC-LCIS)

(*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.

- **LABEL:** RALOXIFENE HYDROCHLORIDE tablet, coated (**DailyMed:** https://dailymed.nlm.nih.gov) (G-1)
- **LABEL:** RALOXIFENE HYDROCHLORIDE tablet, coated (**DailyMed:** https://dailymed.nlm.nih.gov) (G-2)

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

The study patients of **Breast Cancer LCIS (BC-LCIS)** will treat raloxifene **without** mastectomy but with enough biopsy tissue and peripheral blood mononuclear cells and follow up the standard of care treatment with drug therapy in the Raloxifene Tablet DAILYMED Label i.e., Recommended Dose for **Breast Cancer LCIS** i.e., Raloxifene Tablet, DAILYMED as first line treatment in patients with breast cancer LCIS (BC-LCIS).

- Criteria:

✧ Recruit 600 patients of **Breast Cancer LCIS** who are suitable for breast tissue biopsy and drawing peripheral blood.
✧ The 600 **Breast Cancer LCIS** patients are randomly separated into 2 groups via computer.
✧ **The usual approach randomization of double-blinding active treatment concurrent control group:**
✓ RALOXIFENE HYDROCHLORIDE tablet, coated (Generic-1) -- 60 mg orally daily (12 weeks)
✧ **The study approach randomization of double-blinding active treatment concurrent control group:**
✓ RALOXIFENE HYDROCHLORIDE tablet, coated (Generic-2) -- 60 mg orally daily (12 weeks)
✧ Every breast cancer LCIS patient will receive breast tissue biopsy.
✧ Keep storing all biopsy breast tissue.
✧ Every breast cancer LCIS patient will receive drawings of peripheral blood.
✧ Keep storing all peripheral blood mononuclear cells.
✧ 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 biopsy breast tissue as follows: **Estrogen Receptor (ER)**.
✧ Sequence precisely each target gene DNA whole chain in peripheral blood mononuclear cells as follows: **UDP-glucuronosyltransferase (UGT)**.
✧ If any participating patients have serious side effects, they will stop the research.
✧ If any participating patients have no therapeutic effects, they will stop the research.

- Inclusion Criteria:

1. Clinical diagnosis of **Breast Cancer showing lobular carcinoma in situ (LCIS) (BC-LCIS)**
2. Clinical biopsy diagnosis of **Breast Cancer showing lobular carcinoma in situ (LCIS) (BC-LCIS)**
3. Suitable for drawing peripheral blood and biopsy
4. Random and double blind
5. Measurable disease
6. Adequate organ functions
7. Adequate performance status
8. Age 24 years old and over
9. Receive blood-drawing and biopsy.
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. Thrombus or Bleed Tendency
9. Serious Risks or Serious Adverse Events of the drug product
10. The prohibition of drug products
11. The participating patients have serious side effects.
12. The participating patients have no therapeutic effects.

### The expected accrual populations:

- ✧ Recruit 600 patients with Breast Cancer LCIS who are suitable for blood-drawing and biopsy.
- ✧ The 600 BC-LCIS patients are randomly separated into 2 groups via computer.
- ✧ The usual approach group is 300 BC-LCIS patients.
- ✧ The study approach group is 300 BC-LCIS patients.
- ✧ Every BC-LCIS patient will receive peripheral blood-drawing and breast tissue biopsy.
- ✧ Keep storing all peripheral blood and biopsy tissue.

### The primary efficacy and safety endpoints:

- After peripheral blood-drawing and breast tissue biopsy for each patient with **breast cancer showing lobular carcinoma in situ (LCIS) (BC-LCIS)**, through usual approach chemotherapy or study approach chemotherapy, in 90-days Phase 2 ANDA SNP Oncology Clinical Trial, there should **not** be cancer growth or cancer metastasis.
- If cancer growth or cancer metastasis appears, stop these patients' trial.
- If serious side effects or serious adverse reactions appear, stop these patients' trial.
- If they have no therapeutic effects, stop these patients' trial.

### The dose range (The statistical table):

- ✧ The usual approach randomization double-blinding active treatment concurrent control group:
- ✓ RALOXIFENE HYDROCHLORIDE tablet, coated (NDC: 71209-082-01) - 60 mg orally daily (12 weeks) (G-1)

| Drug Names | Targets in Breast Tissue | Targets in Peripheral Blood |
|---|---|---|
| Raloxifene Tablet | ER | UGT |

- ✧ The study approach randomization of double-blinding active treatment concurrent control group:
- ✓ RALOXIFENE HYDROCHLORIDE tablet, coated (NDC: 72241-010-22) - 60 mg orally daily (12 weeks) (G-2)

| Drug Names | Targets in Breast Tissue | Targets in Peripheral Blood |
|---|---|---|
| Raloxifene Tablet | ER | UGT |

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

- ✧ 600 BC-LCIS patients will test breast tissue DNA.
- ✓ Every BC-LCIS patient will receive testing for ER Gene SNPs in breast tissue DNA.
- ✧ 600 BC-LCIS patients will test peripheral blood DNA.
- ✓ Every BC-LCIS patient will receive UGT Gene SNPs testing in peripheral blood DNA.

- ✧ Sequence precisely every oncology drug target gene DNA whole chain.
- ✓ Sequence precisely ER gene DNA whole chain in breast tissue …
- ✓ Sequence precisely UGT 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 ER gene DNA whole chain.
- ✓ Find every single nucleotide gene mutation site in UGT gene DNA whole chain.
- ✧ If one single nucleotide gene mutation site appears ratio more than 1% in 600 BC-LCIS patients, this is SNP.
- ✓ Calculate ER Gene SNPs in breast tissue DNA in 600 BC-LCIS patients.
- ✓ Calculate UGT Gene SNPs in peripheral blood DNA in 600 BC-LCIS patients.

- ✧ If the breast biopsy samples of the usual approach group have the same oncology drug target gene SNP as the breast biopsy 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 breast biopsy samples of the usual approach group have the same ER gene SNP as breast biopsy samples of the study approach group, the relationship between this ER gene SNP and this Raloxifene oncology drug efficacy can be confirmed, i.e., this ER gene SNP is related to this Raloxifene oncology drug efficacy.

| Target Gene SNP in Breast Biopsy of Usual Approach Group of a BC-LCIS patient | Target Gene SNP in Breast Biopsy of Study Approach Group of a BC-LCIS patient | Comparing Results |
|---|---|---|
| ER Gene SNP | ER Gene SNP | Same |
| This ER Gene SNP is related to the Raloxifene 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 UGT gene SNP as the peripheral blood samples of the study approach group, the relationship between this UGT gene SNP and this Raloxifene drug risk can be confirmed, i.e., this UGT gene SNP is related to this Raloxifene drug risk.

| Target Gene SNP in Peripheral Blood of Usual Approach Group of a BC-LCIS patient | Target Gene SNP in Peripheral Blood of Study Approach Group of a BC-LCIS patient | Comparing Results |
|---|---|---|
| UGT gene SNP | UGT gene SNP | Same |
| This UGT Gene SNP is related to the Raloxifene drug risk. | | |

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

The study patients will be treated the **Breast Cancer (BC-LCIS)** with Raloxifene without mastectomy. The ANDA SNP investigation will follow up the standard of care treatment with drug therapy in the RALOXIFENE HYDROCHLORIDE tablet, coated DAILYMED Label.

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 IRB determination, when I conduct my clinical investigation **(NCT06062810)**.

**Reference:**


- **LABEL:** RALOXIFENE HYDROCHLORIDE tablet, coated (**DAILYMED:** https://dailymed.nlm.nih.gov) (G-1)
- **LABEL:** RALOXIFENE HYDROCHLORIDE tablet, coated (**DAILYMED:** https://dailymed.nlm.nih.gov) (G-2)


**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 (NCT06062810).

**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 (NCT06062810) 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 (NCT06062810).

The investigation (**NCT06062810**) will be conducted in compliance with the requirements for **21 CFR Part 56** as follows:

**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 (NCT06062810), i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject.

Our investigation (**NCT06062810**) will be conducted in compliance with the requirements for **21 CFR Part 50** as follows:

**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 (NCT06062810), 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)
  - 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)
- **ClinicalTrials.gov ID: NCT06062810** 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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