LAY SUMMARY OF KRT-232-111: CLINICAL STUDY RESULTS

This report provides the results of only this study. Researchers must look at the results of many types of studies to understand if a study medication works, how it works, and if it is safe to prescribe to persons with the disease.

CLINICAL STUDY INFORMATION

Study Name

An Open-Label, Multicenter, Phase 1b/2 Study of the Safety and Efficacy of Navtemadlin (KRT-232) in Combination with Acalabrutinib in Subjects with Relapsed/Refractory Diffuse Large B-cell Lymphoma or Relapsed/Refractory Chronic Lymphocytic Leukemia

Protocol Number

KRT-232-111

Clinical Trial Sponsor

Kartos Therapeutics, Inc.
275 Shoreline Drive, Suite 300
Redwood City, CA 94065

EU Trial Number

Eudra CT: 2020-002464-31

Other Identifiers

ClinicalTrials.gov: NCT04502394

Abstract

Purpose of the study: To see if navtemadlin in combination with acalabrutinib is safe and effective for the treatment of patients with previously treated diffuse large B-cell lymphoma (DLBCL) and chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL).

What was tested:

Researchers tested different doses of navtemadlin, along with a consistent dose of acalabrutinib, to find the safest dose and see if the combination could help subjects. The study had two parts:

- Phase 1b: Tested different doses to find the safest dose for patients.
- Phase 2: Looked at whether the combination of drugs could help slow or combat the cancers

People taking part: A total of 49 subjects, aged 29 to 91, with previously treated DLBCL or CLL/SLL from 10 countries took part in the trial.

Results: The combination of navtemadlin and acalabrutinib was effective for some participants, helping to reduce the number of cancer cells in their bodies.

Safety: Overall, the combination of navtemadlin and acalabrutinib was well-tolerated by patients, and no unexpected side effects were reported.

GENERAL INFORAMTION ABOUT THE TRIAL

Where was the study done?

The trial took place in 10 countries including, Australia, Belgium, Czech Republic, Italy, South Korea, Poland, Portugal, Switzerland, United Kingdom, and the United States.

When was the study done?

The study started in February 2021 and ended in April 2024. The study was closed early by the sponsor for business reasons and not because of any safety concerns.

What was the main objective of the study?

This study aimed to determine if a combination of the drugs navtemadlin and acalabrutinib is safe and effective in treating people with certain blood cancers, specifically diffuse large B-cell lymphoma (or DLBCL) and chronic lymphocytic leukemia/small lymphocytic lymphoma (or CLL/SLL), who had already received other treatments. It was also used to determine the highest dose of navtemadlin that subjects can safely take in combination with acalabrutinib without having severe side effects for use in the next phase of development and future studies.

This was an "open-label" study, meaning both the researchers and the subjects were aware of the drug or treatment being given. This study was conducted globally in 2 parts: **Phase 1b** and **Phase 2**.

Phase 1b: Finding the Safe Dose

In the Phase 1b part of the study, the main goal was to determine the highest safe dose of navtemadlin. Other goals in Phase 1b was to find out what the side effects were, what happens to the drug in the body, and if the treatment helps to combat the cancer when given with a fixed dose of acalabrutinib (100 mg by mouth twice daily continuously). Navtemadlin was given at increasing dose levels (120 mg, 240 mg, 300 mg, and 360 mg) along with a fixed dose of acalabrutinib (100 mg taken twice daily). The doses were tested in groups of 3 subjects. If the first group tolerated a dose without a severe side effect (called "dose-limiting toxicity"), the next group received a slightly higher dose. This continued until either a side effect prevented further increases or the maximum planned dose was reached. The dose levels of navtemadlin tested were taken by mouth once a day for 7 days every 28 days. At the end of Phase 1b, researchers looked at the results of Phase 1b to decide which navtemadlin dose to use during Phase 2.

Phase 2: Testing Effectiveness and Continued Safety

In Phase 2, researchers aimed to find out if navtemadlin and acalabrutinib together could combat or control cancer. Subjects were divided into two groups based on their type of cancer:

- Group 1: Subjects with DLBCL
- Group 2: Subjects with CLL/SLL

The combination was considered effective if subjects experienced either:

- Complete Response (CR): No visible signs of cancer after treatment
- Partial Response (PR): A significant reduction in cancer burden

Researchers also tracked how long subjects lived with their cancer without it getting worse (progression-free survival) and how long any responses lasted (duration of response).

Which medicines were studied?

The investigational drug navtemadlin in combination with the FDA-approved drug Calquence® (acalabrutinib) were studied. Navtemadlin blocks the function of a drug called MDM2, resulting in increased self-destruction of cancer cells in the body. Acalabrutinib blocks the function of a protein called BTK, resulting in decreased production and survival of specific cancer cells. In this study, navtemadlin was tested at different dose levels to find the best dose for safety and effectiveness, while acalabrutinib was given at the standard dose already approved for treating certain cancers like CLL/SLL and previously-treated mantle cell lymphoma (MCL).

Who participated in the study?

A total of 49 people participated in this study; 29 men and 20 women, mostly over the age of 65, ranging from 29 to 91 years old. Participants included adults with certain blood cancers (DLBCL or CLL/SLL) that had either come back (relapsed) or stopped responding to previous treatments (refractory). To join, participants had to:

- Be at least 18 years old with a measurable disease that required treatment.
- Have an unmutated *TP53* gene, meaning it functioned normally.
- Not have previously received certain drugs called MDM2 or BTK inhibitors.

Study Structure

The study was conducted in two parts, Phase 1b and Phase 2, with each phase testing the combination treatment on different groups of participants:

- Phase 1b: A total of 30 participants (15 each in Group 1 and Group 2) received the study drug at varying doses to find the safe dose. This group included 13 men and 9 women, ages 29 to 91, mostly over 65.
- Phase 2: Nineteen participants (7 in Group 1 and 12 in Group 2) received the recommended dose from Phase 1b. This group included 16 men and 11 women, aged 44 to 88, also mostly over 65.

Study Completion and Treatment Discontinuation

The study has been completed, and all participants have exited. Reasons for stopping the treatment differed between groups:

- Group 1: Most participants (13 out of 22) stopped because their cancer worsened.
- Group 2: Common reasons for stopping included side effects (12 out of 27 participants) and the sponsor's decision to end the study early (22 out of 27 participants). Sadly, a few participants in Group 2 (13 out of 22) also stopped due to death.

WHAT WERE THE OVERALL STUDY RESULTS?

What were the side effects?

Side effects are unwanted medical events (like nausea) that occur during the study. A side effect is considered "serious" if it is life-threatening, requires hospitalization, or causes lasting health issues.

All side effects were recorded in this study, even if the researchers did not think they were related to study treatment. Side effects that occurred during Phase 1 that were based on the dose strength (known as dose-limiting toxicities) were also recorded.

Group 1 (DLBCL):

- **Dose-Limiting Side Effects**: no serious side effects were found at the lower doses (120 mg and 240 mg of navtemadlin). At the highest dose (360 mg), one subject experienced a prolonged low neutrophil count
- **Common Serious Side Effects** (reported in 2 subjects or more):
  - Worsening DLBCL and worsening of general physical health (2 subjects each)
  - Other serious side effects linked to navtemadlin, acalabrutinib or both included anemia (low red blood cells), pneumonia (lung infection), atrial fibrillation (irregular heartbeat), and food intolerance (1 subject each)
- **Frequent Side Effects** (reported in over 20% of subjects)
  - Anemia and low platelet count (15/22 subjects each, or 68%)
  - Diarrhea, nausea, and low neutrophil count (13/22 subjects each, or 59%)
  - Vomiting (8/22 subjects, or 36%)
  - Constipation, loss of appetite, and fatigue (7/22 subjects each, or 32%)
  - Swelling in limbs (6/22 subjects, or 27%)
  - Breathing difficulties and headache (5/22 subjects each, or 23%)
- **Severe Cases:** One subject had a fatal case of bacterial pneumonia that the researcher believed was related to both navtemadlin and acalabrutinib.
- **Treatment was stopped:** 5 subjects stopped taking the treatment because of side effects

During Phase 1b, the Safety Review Committee (SRC) analyzed these side effects. They determined that a lower dose (300 mg) would be used in Phase 2 because of the side effects seen at the 360 mg dose

Side Effects in Group 2 (CLL/SLL) Included:

Group 2 (CLL/SLL)

- **Dose-Limiting Side Effects**: No dose-limiting side effects occurred at any dose level.
- **Common Serious Side Effects**:
  - *Colitis* (inflammation of the colon) and *pneumonia* (2 subjects each)

  - Other serious side effects related to the study treatment included COVID-19 pneumonia, liver infection, colitis, low neutrophil count with fever, pericarditis (inflammation around the heart), and dehydration (1 subject each).

- **Frequent Side Effects** (Reported in Over 20% of Subjects):
  - Nausea (22/29 subjects, or 82%)
  - Diarrhea (18/29 subjects, or 67%)
  - Vomiting (14/29 subjects, or 52%)
  - Constipation and headache (13/29 each, or 48%)
  - Low platelet count and low neutrophil count (12/29 subjects each, or 44%)
  - Anemia (9/29 subjects, or 33%)
  - Fatigue (8/29 subjects, or 30%)
  - Cough (7/29 subjects, or 26%)
  - Abdominal pain (6/29 subjects, or 22%)
- **Severe Cases**: No fatal serious side effects were reported
- 12 subjects (44%) stopped taking the treatment due to side effects.

Overall Findings on Side Effects

The side effects experienced in both groups were consistent with those expected in participants with DLBCL and CLL/SLL, and with the known effects of navtemadlin and acalabrutinib.

Did the drug work?

Effectiveness in Group 1 (DLBLC)

This study measured if different doses of navtemadlin, combined with acalabrutinib, impacted a subject's response to treatment – that is, reduced the number of cancer cells in subjects' bodies. Responses could be partial (some reduction in the number of cancer cells) or complete (no evidence of cancer cells remaining in the body). Here's what researchers found:

- Responses by Dose Level:
  - **120 mg**: None of the 5 subjects had a response (0%).
  - **240 mg**: 1 out of 3 subjects (33%) had a response.
  - **300 mg**: 2 out of 7 subjects (29%) had a response.
  - **360 mg**: 4 out of 7 subjects (57%) had a response.

In total, 3 complete responses were reported: 1 at the 240 mg dose and 2 at the 360 mg dose.

Among those who experienced complete responses to treatment:

- At the 240 mg dose, the response lasted 20.5 months.
- At the 360 mg dose, the response lasted an average of nearly 3 months.

The study also looked at progression-free survival (or PFS), the amount of time subjects could live without their cancer getting worse:

- **120 mg**: Cancer stayed stable for an average of 1.6 months.
- **240 mg**: Cancer stayed stable for an average of 1.8 months.
- **300 mg**: Cancer stayed stable for an average of 3.3 months.
- **360 mg**: Cancer stayed stable for an average of 3.5 months.

Overall, navtemadlin given with acalabrutinib was effective at 240 mg, 300 mg, and 360 mg doses, with higher doses generally showing better results.

Effectiveness in Group 2 (CLL/SLL)

This study measured how well different doses of navtemadlin, given with acalabrutinib, helped reduce the number of cancer cells in subjects. Responses were considered "complete" (CR), "complete with partial bone marrow recovery" (CRi), "partial response" (PR), or "nodular partial response" (nPR). Here's what the study found:

- Response Rates by Dose Level:
  - **120 mg**: 100% (3 out of 3 subjects) showed a response.
  - **240 mg**: 86% (18 out of 21 subjects) showed a response.
  - **300 mg**: 67% (2 out of 3 subjects) showed a response.

Among those receiving the 240 mg dose, 15% (4 out of 21 subjects) achieved a CR or CRi.

Progression-Free Survival

Progression-free survival (how long subjects live without the disease worsening) was not measured in this group due to very few cases of the disease progressing.

Overall Findings

Navtemadlin combined with acalabrutinib was effective at all three doses (120, 240, and 300 mg), with the best reduction in disease seen at the 240 mg dose compared to the 120 mg dose.

DETAILS OF ANY FURTHER RESEARCH PLANNED?

No additional research measuring navtemadlin effects on these cancers is planned at this time.

WHERE CAN I LEARN MORE ABOUT THIS STUDY?

Kartos Therapeutics, Inc
Contact information:
Name: John Mei
Phone Number: +1 650 542 0136
Email: jmei@kartosthera.com