What patients should know about

ENESTop

Evaluating Nilotinib Efficacy and Safety in Clinical Trials

TFR
TREATMENT-FREE REMISSION STUDY
NOVARTIS ONCOLOGY

Answers to frequently asked questions patients may have about the study of and treatment with nilotinib

1. What is ENESTop?

ENESTop is a clinical study designed to determine the rate of successful treatment-free remission (TFR) within 12 months of cessation of chronic myeloid leukemia (CML)-related treatment in patients who have achieved and maintained a deep molecular response on nilotinib after switching to nilotinib from imatinib. Deep molecular response is defined as achieving a 4.5-log reduction in levels of BCR-ABL transcripts, known as molecular response 4.5, or MR4.5. Patients with an MR4.5 have a disease burden of ≤0.0032% BCR-ABL remaining in the body.

2. What is nilotinib?

Nilotinib belongs to a family of drugs called tyrosine kinase inhibitors (TKIs), which also includes imatinib. These drugs block the BCR-ABL protein, the cause of Philadelphia chromosome-positive chronic myeloid leukemia (Ph+ CML). Nilotinib has been found to be effective and well tolerated in patients with Ph+ CML in the chronic phase (CP) and in the accelerated phase (AP) who were resistant to or intolerant of imatinib. It has also been found to be safe and well tolerated in patients with newly diagnosed Ph+ CML.

3. How does nilotinib differ from imatinib?

Both nilotinib and imatinib target proteins called tyrosine kinases, particularly the BCR-ABL protein. Nilotinib is a next-generation tyrosine kinase inhibitor (TKI) developed to be a potent and selective inhibitor of the BCR-ABL protein, in order to block the signal that causes growth of chronic myeloid leukemia (CML) cells.

Imatinib was approved for use in CML in 2001 and is currently used to treat all phases of CML. Nilotinib was approved for CML in 2007 and is currently used to treat newly diagnosed Philadelphia chromosome-positive (Ph+) CML in the chronic phase (CP). It is also used to treat Ph+ CML in CP and accelerated phase (AP) in adult patients resistant to or intolerant of prior therapy including imatinib.

Stopping treatment in CML is not a current clinical recommendation in any standard treatment guidelines and should only be attempted in the context of a well-conducted clinical trial. This is strictly an investigational study at this time.

4. What is treatment-free remission (TFR)?

TFR is when a patient has achieved such a low level of leukemic cells, or sustained deep molecular response, that he/she no longer needs drug therapy. In order to be eligible for stopping nilotinib therapy, a patient must achieve and maintain a deep molecular response (BCR-ABL ≤0.0032% International Scale, or MR4.5) for at least 1 year.

5. How often will I need to see my doctor during the treatment portion of the study?

Once enrolled in this study, all patients will receive 1 year of nilotinib treatment to ensure deep molecular response is maintained. During this year, patients will be seen at Weeks 1, 12, 24, 36, 48, and 52 (within 7 days of the last dose of study medication) for scheduled visits and polymerase chain reaction (PCR) tests.

6. How will my doctor know if I am able to stop treatment as part of the study?

If a patient maintains a deep molecular response, MR4.5, throughout the first year, he/she will be eligible to start the nilotinib treatment-free remission (TFR) phase of the study.

Doctors use a simple and convenient blood test called polymerase chain reaction (PCR) to measure levels of BCR-ABL. If a patient has a PCR result above MR4.5 or the sample is missing or not done, a new sample must be collected within 4 weeks. A patient with 2 consecutive PCR results above MR4.5 will not be eligible to enter the TFR phase and will continue on nilotinib treatment.

7. How often will I need to see my doctor after I stop taking the drug?

After stopping nilotinib, patients will have a physical exam every 12 weeks. In addition, polymerase chain reaction (PCR) tests will occur every 4 weeks for the first year (study year 2), every 6 weeks for the second year (study year 3), and every 12 weeks for years 3 and 4 (study years 4 and 5).

8. How long will the ENESTop study last?

The ENESTop study will last for approximately 5 years. There are 2 main phases of the study:

1. The first phase lasts for 1 year. All patients will be treated with nilotinib at the same dose they were taking before entering the study. This is called the "nilotinib consolidation phase."
2. During the second phase of the study, eligible patients will stop taking nilotinib and will be monitored for up to 4 years. This phase of the study is called the "nilotinib treatment-free remission (TFR) phase." After the end of the study, all patients will continue their molecular monitoring as per standard of care at the time with or without chronic myeloid leukemia (CML) therapy.

9. What tests will my doctor order during the study?

In addition to a physical examination, safety and tolerability assessments, vital signs, etc, the following will be ordered:

- Polymerase chain reaction (PCR), a simple and convenient blood test to measure molecular response (MR)
- Bone marrow testing only when a patient has a loss of major molecular response (MMR) or when a patient's BCR-ABL has risen to >0.1% International Scale (equivalent to loss of complete cytogenetic response [CCyR]), or when a patient has loss of complete hematologic response (CHR)
- Standard blood biochemistry and hematology tests that are routinely done in all patients as a standard of care
- Cardiac assessment with electrocardiogram (ECG) once per year when a patient is taking nilotinib, or on the same day before a patient restarts nilotinib, or as needed

10. Am I allowed to take other medications while I am enrolled in the study?

Yes; however, all previous and new medications and significant non-drug therapies in both the treatment phase and the treatment-free remission (TFR) phase must be reported to the study doctor, as he/she will need to report all concomitant medications within this study.

Patients must notify the study doctor about any new medications taken.

11. What should I do if I miss a dose of treatment medication during the study?

Contact your doctor if you miss a dose of nilotinib during the "treatment phase" of the study.

12. What happens if I experience side effects during the study?

Patients may experience side effects while taking nilotinib. They must report any adverse event to their doctor, who will evaluate its severity, duration, and relation to study treatment so that the appropriate action may be taken. This may include dose adjustment, interruption, or discontinuation of the drug.

13. Does treatment-free remission (TFR) mean I am cured of my disease?

Achieving TFR means that there is no need to take nilotinib or any other chronic myeloid leukemia (CML) therapy. This does not mean that all leukemic cells have been eradicated from a patient's body. This is the reason why all patients will need to continue at least quarterly molecular monitoring. Results of these tests will indicate if the patient can remain treatment-free or needs to be restarted on nilotinib. Nilotinib treatment will need to be restarted when a patient experiences a loss of major molecular response (MMR) (BCR-ABL >0.1% International Scale) or confirmed loss of MR4 (BCR-ABL >0.01% on 2 consecutive tests).

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14. What happens if my disease comes back after I stop taking the study medication? Will I be able to re-enter the treatment portion of the study?

Molecular response (MR) may change over the drug-free study period. If loss of molecular response occurs, treatment with nilotinib can be restarted.

To keep track of patients' molecular response, BCR-ABL levels are tested every 4 weeks during year 2 of the study, every 6 weeks during year 3, and every 12 weeks during years 4 and 5. Loss of molecular response is defined as 2 consecutive BCR-ABL results confirming loss of MR4 or loss of major molecular response (MMR); this will trigger restarting nilotinib immediately. Based on previous clinical trial results, patients are expected to regain molecular response lost after stopping imatinib or nilotinib.

15. What happens to me when the ENESTop study is completed?

The end of the study occurs 4 years after the last patient in the study enters the nilotinib treatment-free remission (TFR) phase. At that time, a patient will be eligible to continue on a roll-over study in order to receive treatment with nilotinib. This treatment will continue for as long as he/she continues to demonstrate benefit and does not experience unacceptable toxicities, or until nilotinib is commercially available in the patient's country of residence.

16. If I am not eligible to stop taking nilotinib (enter the treatment-free remission [TFR] phase), what will happen to me?

Patients who are not eligible to enter the TFR phase will continue to be treated with nilotinib on study for another year with quarterly polymerase chain reaction (PCR) tests and physical examinations. If a patient maintains a deep molecular response, MR4.5, throughout the second year of treatment, he/she will have another chance to stop treatment and enter the TFR-2 phase.

Glossary

MMR, MR3 - Major molecular response; achieving a 3-log reduction (1000 times) in levels of BCR-ABL (BCR-ABL ≤0.1% International Scale [IS])

MR4 - Deep molecular response; achieving a 4-log reduction (10,000 times) in levels of BCR-ABL (BCR-ABL ≤0.01% IS)

MR4.5 - Deep molecular response; achieving a 4.5-log reduction (10,500 times) in levels of BCR-ABL (BCR-ABL ≤0.0032% IS)

TFR - Treatment-free remission; stable residual chronic myeloid leukemia (CML) without any CML-related treatment

Remission - Reduction of the tumor load

BCR-ABL - CML-specific genetic change that causes CML

PCR - Polymerase chain reaction, a specific diagnostic test carried out on venous blood that is able to detect the CML-specific BCR-ABL gene in a very sensitive way

Ph+ CML - CML where the Philadelphia chromosome can be detected

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