NAUT study: Multicenter prospective trial after first or second unsuccessful treatment discontinuation in chronic myeloid leukemia estimating the efficacy of nilotinib in inducing the persistence of molecular remission after stopping TKI 2nd time or 3rd time

Published: 23-01-2017
Last updated: 08-02-2025

Assessment of duration of MMR or better after stopping TKI therapy a second or third time in patients with at least three years prior TKI treatment comprising at least two years of nilotinib treatment and maintained stable MR4 for at least one year...

Ethical review	Approved WMO
Status	Completed
Health condition type	Leukaemias
Study type	Interventional

Summary

ID

NL-OMON52992

Source
ToetsingOnline

Brief title
NAUT study CML

Condition

- Leukaemias
- Leukaemias

Synonym

chronic myeloid leukemia

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit van Heidelberg
Source(s) of monetary or material Support: Novartis,universiteit van Heidelberg en farmaceutische industrie.,Universteit van Heidelberg

Intervention

Keyword: 2nd stop, 3rd stop, CML-CP, stop nilotinib

Outcome measures

Primary outcome

The primary endpoint is molecular relapse-free survival, measured at 12 months

and 36 months after 2nd stop or 3rd stop.

Secondary outcome

- number of patients who re-achieved stable MR4.5, and were proposed a 2nd stop

or 3rd stop

- number of patients who accepted/refused 2nd stop or 3rd stop 2 and 3 years

after study entry; whereas stable MR4.5 is defined as two PCRs during 6 months

before stopping demonstrating MR4.5

- safety profile, tolerability and AEs under nilotinib treatment

- QoL profiles under nilotinib treatment and comparison with previous TKI

therapy before switch and after stopping

- overall and progression-free survival, and probabilities of a restart of TKI

treatment without prior molecular relapse

- Time to re-achievement of MR4.5 after restart of therapy

- incidence of any AEs (e.g. from musculoskeletal system) that arise after

stopping TKI treatment a second time

Study description

Background summary

Results of the STIM studies showed that stopping of the TKI intake did not endanger patients; most patients who experienced molecular relapse did so within 6 months of imatinib cessation and remained responsive to re-treatment with imatinib as observed in the pilot study.
In the EURO-SKI study, a majority of the patients have undergone treatment with imatinib first-line with more than 90% of patients in the interim analysis. Actually, among the first 200 eligible patients with at least 6 months of follow-up, 123 patients remained without molecular relapse defined as loss of MMR at one time point.

So far, only limited experience is available with second generation TKIs and for patients who stopped a second time or third time after molecular relapse in a first or second treatment-free phase.

The first-line studies of nilotinib (ENESTnd) in newly diagnosed patients indicated that nilotinib induces faster and deeper molecular responses than imatinib. Although, up to now, this has not translated into a survival advantage, it is possible, but not yet shown, that this might result in higher rates of successful discontinuation.

Study objective

Assessment of duration of MMR or better after stopping TKI therapy a second or third time in patients with at least three years prior TKI treatment comprising at least two years of nilotinib treatment and maintained stable MR4 for at least one year and MR4.5 for at least 6 months before stopping in patients -
- who failed a first stop in the EURO-SKI study (standardized criteria)
-- who failed a first stop or second stop outside the EURO-SKI study but would have had fulfilled same eligible criteria and were stopped according to EURO-SKI criteria
-- who failed a first stop or second stop outside the EURO-SKI study without fulfilling EURO-SKI criteria

Study design

Study is an open label, prospective, uncontrolled multicenter trial.

Intervention

- a Nilotinb treatment phase for 24 months
- Treatment -Free Remission (TFR) phase, if patient has re-achieved a MR4 for at least 1 year and MR4.5 for at least 0.5 year.

Study burden and risks

As no treatment is given, it is possible to expect some quality of life benefit, especially in patients that have suffered side effects on TKI treatment. At least in part of patients the benefit will be to be off therapy for a longer period than 6 months.

Risks for nilotinib treatment phase:
Nilotinib is approved for first-line therapy in CML and the toxicity profile is well known as the drug is in clinical use since 2006.
No additional risk is predictable; to manage potential toxicity 3-monthly visits are indicated within the study.

Risks for the treatment free remission phase:
In EURO-SKI, trial a withdrawal syndrome was described in about 15-20% of patients after stopping imatinib.
As has been seen after stopping for the first time, myalgia and arthralgia, especially in the upper arms and shoulders may also be expected to occur at a second stop trial. In general this is a benign phenomenon, not requiring therapy. However, in a few cases, it has been necessary to treat this pain syndrome with corticosteroids. These may also have adverse effects, like mood disorders, induction of diabetes mellitus, osteoporosis and immune suppression.

Burden in the treatment free remission phase is once a month hospital visit and blood collection for close monitoring of residual disease by qRT-PCR after stopping TKI, the first 6 months after stopping, followed by 6 weeks visits in the next 6 months.

Contacts

Public
Universiteit van Heidelberg

Seminarstraat 2
Heidelberg 69115
DE
Scientific

Universiteit van Heidelberg

Seminarstraat 2
Heidelberg 69115
DE

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

· Age >= 18 years
· Patients with Ph -chromosome and/or the BCR-ABL fusion gene (either b3a2 and/or b2a2) positive CML
· CML in CP having failed prior attempt(s) to stop imatinib or other TKIs therapy either within EURO-SKI or not
· Pretreatment at least one year with any TKI after 1st or 2nd stop
· Written informed consent

Exclusion criteria

· Previous hematological relapse after first or second stop of TKI.
· Failure to any TKI at any time during CML treatment TKI according to actual ELN criteria
· Previous planned or performed allo SCT
· Previous AP/BC at any time in the history of the disease
· High cardiac risk according to ESC Score
· Contraindication against nilotinib (see following)
· Impaired cardiac function including any of the following:
o Use of a ventricular paced pacemaker; congenital long QT syndrome or family history of; history or presence of significant ventricular or atrial tachyarrhythmias; clinically significant resting bradycardia (<50 bpm); QTcF

>450 msec at baseline, myocardial infarction before baseline; other clinically significant heart disease (e.g., unstable angina, congestive heart failure, or uncontrolled hypertension).
· Treatment with inhibitors of CYP3A4 or medications that have been well documented
to prolong the QT interval is contraindicated.
· History of acute pancreatitis within one year of study entry or medical history of chronic pancreatitis.
· Positive hepatitis B virus serology test or HBV infection.
· Any other malignancy except if neither clinically significant nor requires active intervention.
· Severe or uncontrolled medical conditions (i.e., uncontrolled diabetes, acute or chronic liver disease, pancreatic, or severe renal disease unrelated to tumor, active or uncontrolled infection).
· Women who are pregnant, breast feeding, or of childbearing potential without a negative serum pregnancy test at baseline.
Male or female patients of childbearing potential unwilling to use an effective barrier contraceptive method.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	27-07-2017
Enrollment:	15
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Tasigna

Generic name:	nilotinib
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	23-01-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-07-2017
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	16-07-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-01-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	22-07-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2022
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2015-004998-33-NL
ClinicalTrials.gov	NCT02917720
CCMO	NL59532.029.16