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Trial record **1 of 1** for: Endure (ENDURE-CML-IX)

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ENDURE - Efficacy and Safety of AOP2014 With CML Patients in Remission (ENDURE-CML-IX)

This study is currently recruiting participants.

See [▶ Contacts and Locations](#)

Verified April 2017 by Philipps University Marburg Medical Center

Sponsor:


Philipps University Marburg Medical Center

ClinicalTrials.gov Identifier:

NCT03117816

First Posted: April 18, 2017

Last Update Posted: August 22, 2017

 The safety and scientific validity of this study is the responsibility of the study sponsor and investigators. Listing a study does not mean it has been evaluated by the U.S. Federal Government. [Know the risks and potential benefits](#) of clinical studies and talk to your health care provider before participating. Read our [disclaimer](#) for details.

Collaborators:

Deutsche Krebshilfe e.V., Bonn (Germany)

AOP Orphan Pharmaceuticals AG

Information provided by (Responsible Party):

Philipps University Marburg Medical Center

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[No Study Results Posted](#)

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[▶ Purpose](#)

A randomized, open-label assessor blinded, multi-center, controlled phase II Trial to evaluate the efficacy of AOP2014 administered bi-weekly subcutaneously (s.c.) in preventing molecular relapse (loss of MMR) in CML patients, who discontinue ABL tyrosine kinase inhibitor therapy (TKI) in deep molecular remission of MR4 or better (MR4.5, or MR5).

<u>Condition</u>	<u>Intervention</u>	<u>Phase</u>
Chronic Myeloid Leukemia in Remission	Drug: AOP2014 / Pegylated-Proline-interferon alpha-2b Other: Surveillance	Phase 2

Study Type: Interventional

Study Design: Allocation: Randomized

Intervention Model: Parallel Assignment

Masking: Single (Outcomes Assessor)

Masking Description:

A randomized, open-label assessor blinded, multi-center, controlled phase II trial

Primary Purpose: Prevention

Official Title: Efficacy and Safety of Pegylated Proline Interferon Alpha 2b (AOP2014) in Maintaining Deep Molecular Remissions in Patients With Chronic Myeloid Leukemia (CML) Who Discontinue ABL-Kinase Inhibitor Therapy - a Randomized Phase II, Multicenter Trial With Post-study Follow-up

Resource links provided by NLM:

[Genetics Home Reference](#) related topics: [chronic myeloid leukemia](#)

[MedlinePlus](#) related topics: [Chronic Myeloid Leukemia](#) [Leukemia](#)

[Drug Information](#) available for: [Proline](#) [Interferon](#) [Interferon Alfa-2b](#)

[Genetic and Rare Diseases Information Center](#) resources: [Myeloid Leukemia](#)
[Chronic Myeloid Leukemia](#) [Chronic Myeloproliferative Disorders](#)

[U.S. FDA Resources](#)

Further study details as provided by Philipps University Marburg Medical Center:

Primary Outcome Measures:

- RFS 7 [Time Frame: Month 7]

The primary efficacy endpoint is molecular relapse free survival, RFS, at month 7 after randomization. Relapse is defined as loss of major molecular remission, MMR, which is any increase of the BCR-ABL ratio to > 0.1% according to the international scale (IS). Time to relapse is defined as the time from randomization to relapse

Secondary Outcome Measures:

- RFS 13 [Time Frame: Month 13]

The relapse free survival, RFS, at month 13 after randomization

- RFS 25 [Time Frame: Month 25]

The relapse free survival, RFS, at month 25 after randomization

- Number of participants with treatment-related adverse events as assessed by CTCAE v4.03 [Time Frame: Day 0 - Month 18]

Adverse events, serious adverse events (AEs, SAEs)• Safety, tolerability and toxicity based on incidences of adverse events, serious adverse events, frequency of clinical laboratory tests by worst toxicity grade

- Quality of life measured by EORTC QLQ-C30 [Time Frame: Day 0 - Month 18]

The data will be compared between the treatment groups and to QoL of normal population.

- Quality of life measured by EORTC-QLQ-CML24 [Time Frame: Day 0 - Month 18]

The data will be compared between the treatment groups and to QoL of normal population. Furthermore, results of the CML24 module should be shared with the EORTC group to complete the validation of this questionnaire

- detection of blood parameter 95 CD86+pDC as RFS predictor [Time Frame: Day 0 - Month 25]

To validate the value of 95 CD86+pDC / 105 lymphocytes at baseline (before TKI stop) as a predictor of RFS

- OS (overall survival) [Time Frame: Day 0 - Month 25]

Overall survival (OS), defined as the time between the date of randomization and the date of death from any cause.

Estimated Enrollment: 214
 Actual Study Start Date: May 4, 2017
 Estimated Study Completion Date: December 2024
 Estimated Primary Completion Date: September 2021 (Final data collection date for primary outcome measure)

<u>Arms</u>	<u>Assigned Interventions</u>
<p>Experimental: investigational arm A</p> <p>There will be an overlapping treatment with AOP2014 and TKI for one month. After one month, the TKI therapy will be stopped and patient will receive only AOP2014 treatment for the next 14 months.</p>	<p>Drug: AOP2014 / Pegylated-Proline-interferon alpha-2b</p> <p>AOP2014 as pre-filled auto-injection pen for subcutaneous injection, containing 250 µg AOP2014 / 0.5 ml. The solution also contains inactive ingredients (sodium chloride, polysorbate 80, benzyl alcohol, sodium acetate, and acetic acid). The solution is colorless to light yellow.</p>
<p>surveillance arm B</p> <p>This is an open-label study with a "no treatment/ surveillance" group as comparator arm.</p> <p>Similar as in the arm A, patient will discontinue TKI therapy one month after randomization. From then on patient will receive no further treatment.</p>	<p>Other: Surveillance</p> <p>For patients randomized into this treatment arm stopp their standard treatment and will just be under observation.</p>

Detailed Description:

Four hypotheses are tested in hierarchical order. To avoid inflation of type 1 error (false rejection of a null hypothesis), further confirmatory testing has to be stopped as soon as a null hypothesis could not be rejected.

All four hypotheses are tested at significance level 0.05. Null hypotheses 1, 2, and 4 deal with probabilities of molecular relapse-free survival 7, 13, and 25 months after randomisation, respectively; arms A and B are compared with the uncorrected chi-square test. Null hypothesis 3 investigates molecular relapse-free survival as a time-to-event variable; the two arms are compared with the log-rank test

► Eligibility

Information from the National Library of Medicine



Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the contacts provided below. For general information, [Learn About Clinical Studies](#).

Ages Eligible for Study: 18 Years and older (Adult, Senior)
Sexes Eligible for Study: All
Accepts Healthy Volunteers: No

Criteria

Inclusion Criteria:

1. Signed written informed consent form
2. Capability and willingness to comply with study procedures and ability to self-administration of the study drug
3. Male or female aged ≥ 18 years
4. At least three years of TKI therapy
5. BCR-ABL-positive, chronic phase CML patients with a transcript level according to the international scale (IS) of at least MR4, or better (MR4.5, MR5). MR4 is defined as (i) detectable disease $\leq 0.01\%$ BCR-ABL IS or (ii) undetectable disease in cDNA with $\geq 10,000$ ABL or $\geq 24,000$ GUS transcripts for at least one year. There have to be at least three documented PCR-results with MR4 or better within the last year (+/-2 months) before study entry. One of these PCR's must be a confirmatory MR4 measurement prior to randomization by an EUTOS-certified laboratory at the Universities of Mannheim or Jena. No PCR-results in the last year before randomisation can be worse than MR4
6. Patients who had failed to discontinue TKI in a prior discontinuation attempt are eligible for this protocol, if they fulfil criterion 5 after retreatment with TKI. A prior TKI discontinuation failure must be specifically indicated at inclusion and documented
7. Adequate organ function:
especially total bilirubin, lactate dehydrogenase [LDH], aspartate aminotransferase [AST], alanine aminotransferase [ALT] and coagulation parameters $\leq 2 \times$ upper limit of normal (ULN)
8. Adequate hematological parameters:

absolute neutrophil count $\geq 1.2 \times 10^9/L$; platelet count $\geq 100 \times 10^9/L$; leukocyte count $\geq 2.5 \times 10^9/L$; lymphocytes $\geq 1.0 \times 10^9/L$; hemoglobin ≥ 9.0 g/dL or 5.59 mmol/L

9. Female patients with reproductive potential must agree to maintain highly effective methods of contraception by practicing abstinence or by using at least two methods of birth control from the date of consent through the end of the study. If abstinence could not be practiced, a combination of hormonal contraceptive (oral, injectable, or implants) and a barrier method (condom, diaphragm with a vaginal spermicidal agent) has to be used. Also male patients must agree to use condoms during study participation.
10. Negative serum pregnancy test in women of childbearing potential. Urine pregnancy test would also be accepted
11. Date of diagnosis must be known
12. The following parameters from diagnosis must be known:
palpable spleen size enlargement in cm below costal margin, platelet count, percentages of blasts, basophils, and eosinophils in peripheral blood. These values must have been recorded. The values of the Sokal, the EURO, the EUTOS, and the ELTS score would be desirable
13. Tested HIV sero-negativity and tested negative against hepatitis B or C

Exclusion Criteria:

1. History of autoimmune disease
2. Immunosuppressive treatment of any kind
3. Prior allogeneic stem cell Transplantation
4. Prior pegylated IFN therapy. Prior low dose conventional IFN treatment with $\leq 3 \times 3$ Mio I.E. / week for less than 1 year is acceptable
5. Prior history of TKI resistance, accelerated phase or blast crisis
6. Hypersensitivity/allergy to the active substance or excipients of the formulation
7. Severe hepatic dysfunction or decompensated cirrhosis
8. Intake of Telbivudin
9. Thyroid disease that cannot be controlled by conventional therapy
10. Epilepsy or other disorders of the central nervous system
11. Severe cardiac disease history including unstable or uncontrolled cardiac disease in the previous 6 months
12. Any history of retinopathy e.g. retinal detachment, degeneration or thromboembolic events
13. Clinically significant concomitant diseases or conditions, which, in the opinion of the investigator, would lead to an unacceptable risk for the patient to participate in the study (please refer also to the actual Investigator Brochure)

14. Other malignancy, except adequately treated superficial bladder cancer, basal or squamous cell carcinoma of the skin, or other cancer(s) for which the patient has been disease free for more than 3 years
15. Active or uncontrolled infections at the time of randomization
16. Pregnant and/or nursing women
17. Use of antibiotic therapy within the last 2 weeks prior to randomization
18. Concurrent use of molecular targeted therapy
19. Known HIV sero-positivity or known active hepatitis B or C infection
20. Participation in another clinical study with other investigational drugs within 14 days prior to randomization
21. Vaccination within 1 month prior to randomization
22. Any medical, mental, psychological or psychiatric condition (particularly severe depression, suicidal ideation or suicide attempt) that in the opinion of the investigator would not permit the patient to complete the study or comply to study procedures
23. Drug and/or alcohol abuse

▶ Contacts and Locations

Information from the National Library of Medicine



To learn more about this study, you or your doctor may contact the study research staff using the contact information provided by the sponsor.

Please refer to this study by its ClinicalTrials.gov identifier (NCT number):
NCT03117816

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► More Information

Publications:

[Ben-Neriah Y, Daley GQ, Mes-Masson AM, Witte ON, Baltimore D. The chronic myelogenous leukemia-specific P210 protein is the product of the bcr/abl hybrid gene. Science. 1986 Jul 11;233\(4760\):212-4.](#)

[Daley GQ, Van Etten RA, Baltimore D. Induction of chronic myelogenous leukemia in mice by the P210bcr/abl gene of the Philadelphia chromosome. Science. 1990 Feb 16;247\(4944\):824-30.](#)

[Perrotti D, Jamieson C, Goldman J, Skorski T. Chronic myeloid leukemia: mechanisms of blastic transformation. J Clin Invest. 2010 Jul;120\(7\):2254-64. doi: 10.1172/JCI41246. Epub 2010 Jul 1. Review.](#)

[Saussele S, Lauseker M, Gratwohl A, Beelen DW, Bunjes D, Schwerdtfeger R, Kolb HJ, Ho AD, Falge C, Holler E, Schlimok G, Zander AR, Arnold R, Kanz L, Dengler R, Haferlach C, Schlegelberger B, Pffirmann M, Müller MC, Schnittger S, Leitner A, Pletsch N, Hochhaus A, Hasford J, Hehlmann R; German CML Study Group. Allogeneic hematopoietic stem cell transplantation \(allo SCT\) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV. Blood. 2010 Mar 11;115\(10\):1880-5. doi: 10.1182/blood-2009-08-237115. Epub 2009 Nov 18.](#)

Hochhaus A, O'Brien SG, Guilhot F, Druker BJ, Branford S, Foroni L, Goldman JM, Müller MC, Radich JP, Rudoltz M, Mone M, Gathmann I, Hughes TP, Larson RA; IRIS Investigators. Six-year follow-up of patients receiving imatinib for the first-line treatment of chronic myeloid leukemia. *Leukemia*. 2009 Jun;23(6):1054-61. doi: 10.1038/leu.2009.38. Epub 2009 Mar 12. Erratum in: *Leukemia*. 2010 May;24(5):1102.

Larson RA, Hochhaus A, Hughes TP, Clark RE, Etienne G, Kim DW, Flinn IW, Kurokawa M, Moiraghi B, Yu R, Blakesley RE, Gallagher NJ, Saglio G, Kantarjian HM. Nilotinib vs imatinib in patients with newly diagnosed Philadelphia chromosome-positive chronic myeloid leukemia in chronic phase: ENESTnd 3-year follow-up. *Leukemia*. 2012 Oct;26(10):2197-203. doi: 10.1038/leu.2012.134. Epub 2012 May 18.

Jabbour E, Kantarjian HM, Saglio G, Steegmann JL, Shah NP, Boqué C, Chuah C, Pavlovsky C, Mayer J, Cortes J, Baccharani M, Kim DW, Bradley-Garelik MB, Mohamed H, Wildgust M, Hochhaus A. Early response with dasatinib or imatinib in chronic myeloid leukemia: 3-year follow-up from a randomized phase 3 trial (DASISION). *Blood*. 2014 Jan 23;123(4):494-500. doi: 10.1182/blood-2013-06-511592. Epub 2013 Dec 5.

Baccharani M, Deininger MW, Rosti G, Hochhaus A, Soverini S, Apperley JF, Cervantes F, Clark RE, Cortes JE, Guilhot F, Hjorth-Hansen H, Hughes TP, Kantarjian HM, Kim DW, Larson RA, Lipton JH, Mahon FX, Martinelli G, Mayer J, Müller MC, Niederwieser D, Pane F, Radich JP, Rousselot P, Saglio G, Sauße S, Schiffer C, Silver R, Simonsson B, Steegmann JL, Goldman JM, Hehlmann R. European LeukemiaNet recommendations for the management of chronic myeloid leukemia: 2013. *Blood*. 2013 Aug 8;122(6):872-84. doi: 10.1182/blood-2013-05-501569. Epub 2013 Jun 26. Review.

Cross NC, White HE, Müller MC, Saglio G, Hochhaus A. Standardized definitions of molecular response in chronic myeloid leukemia. *Leukemia*. 2012 Oct;26(10):2172-5. doi: 10.1038/leu.2012.104. Epub 2012 Apr 16. Review.

Müller MC, Cross NC, Erben P, Schenk T, Hanfstein B, Ernst T, Hehlmann R, Branford S, Saglio G, Hochhaus A. Harmonization of molecular monitoring of CML therapy in Europe. *Leukemia*. 2009 Nov;23(11):1957-63. doi: 10.1038/leu.2009.168. Epub 2009 Aug 27. Review.

Hehlmann R, Müller MC, Lauseker M, Hanfstein B, Fabarius A, Schreiber A, Proetel U, Pletsch N, Pfirrmann M, Haferlach C, Schnittger S, Einsele H, Dengler J, Falge C, Kanz L, Neubauer A, Kneba M, Stegelmann F, Pfreundschuh M, Waller CF, Spiekermann K, Baerlocher GM, Ehninger G, Heim D, Heimpel H, Nerl C, Krause SW, Hossfeld DK, Kolb HJ, Hasford J, Sauße S, Hochhaus A. Deep molecular response is reached by the majority of patients treated with imatinib, predicts survival, and is achieved more quickly by optimized high-dose imatinib: results from the randomized CML-study IV. *J Clin Oncol*. 2014 Feb 10;32(5):415-23. doi: 10.1200/JCO.2013.49.9020. Epub 2013 Dec 2.

Graham SM, Jørgensen HG, Allan E, Pearson C, Alcorn MJ, Richmond L, Holyoake TL. Primitive, quiescent, Philadelphia-positive stem cells from patients with chronic myeloid leukemia are insensitive to STI571 in vitro. *Blood*. 2002 Jan 1;99(1):319-25.

Corbin AS, Agarwal A, Loriaux M, Cortes J, Deininger MW, Druker BJ. Human chronic myeloid leukemia stem cells are insensitive to imatinib despite inhibition of BCR-ABL activity. *J Clin Invest*. 2011 Jan;121(1):396-409. doi: 10.1172/JCI35721. Epub 2010 Dec 13. Erratum in: *J Clin Invest*. 2011 Mar 1;121(3):1222.

Cortes J, O'Brien S, Kantarjian H. Discontinuation of imatinib therapy after achieving a molecular response. *Blood*. 2004 Oct 1;104(7):2204-5.

Rousselot P, Huguet F, Rea D, Legros L, Cayuela JM, Maarek O, Blanchet O, Marit G, Gluckman E, Reiffers J, Gardembas M, Mahon FX. Imatinib mesylate discontinuation in patients with chronic myelogenous leukemia in complete molecular remission for more than 2 years. *Blood*. 2007 Jan 1;109(1):58-60. Epub 2006 Sep 14.

Mahon FX, Réa D, Guilhot J, Guilhot F, Huguet F, Nicolini F, Legros L, Charbonnier A, Guerci A, Varet B, Etienne G, Reiffers J, Rousselot P; Intergroupe Français des Leucémies Myéloïdes Chroniques. Discontinuation of imatinib in patients with chronic myeloid leukaemia who have maintained complete molecular remission for at least 2 years: the prospective, multicentre Stop Imatinib (STIM) trial. *Lancet Oncol*. 2010 Nov;11(11):1029-35. doi: 10.1016/S1470-2045(10)70233-3. Epub 2010 Oct 19.

Ross DM, Branford S, Seymour JF, Schwarzer AP, Arthur C, Yeung DT, Dang P, Goynes JM, Slader C, Filshie RJ, Mills AK, Melo JV, White DL, Grigg AP, Hughes TP. Safety and efficacy of imatinib cessation for CML patients with stable undetectable minimal residual disease: results from the TWISTER study. *Blood*. 2013 Jul 25;122(4):515-22. doi: 10.1182/blood-2013-02-483750. Epub 2013 May 23.

Rousselot P, Charbonnier A, Cony-Makhoul P, Agape P, Nicolini FE, Varet B, Gardembas M, Etienne G, Réa D, Roy L, Escoffre-Barbe M, Guerci-Bresler A, Tulliez M, Prost S, Spentchian M, Cayuela JM, Reiffers J, Chomel JC, Turhan A, Guilhot J, Guilhot F, Mahon FX. Loss of major molecular response as a trigger for restarting tyrosine kinase inhibitor therapy in patients with chronic-phase chronic myelogenous leukemia who have stopped imatinib after durable undetectable disease. *J Clin Oncol*. 2014 Feb 10;32(5):424-30. doi: 10.1200/JCO.2012.48.5797. Epub 2013 Dec 9.

Branford S, Yeung DT, Ross DM, Prime JA, Field CR, Altamura HK, Yeoman AL, Georgievski J, Jamison BA, Phillis S, Sullivan B, Briggs NE, Hertzberg M, Seymour JF, Reynolds J, Hughes TP. Early molecular response and female sex strongly predict stable undetectable BCR-ABL1, the criteria for imatinib discontinuation in patients with CML. *Blood*. 2013 May 9;121(19):3818-24. doi: 10.1182/blood-2012-10-462291. Epub 2013 Mar 20.

Talpaz M, Kantarjian HM, McCredie KB, Keating MJ, Trujillo J, Gutterman J. Clinical investigation of human alpha interferon in chronic myelogenous leukemia. *Blood*. 1987 May;69(5):1280-8.

Talpaz M, Kantarjian HM, McCredie K, Trujillo JM, Keating MJ, Gutterman JU. Hematologic remission and cytogenetic improvement induced by recombinant human interferon alpha A in chronic myelogenous leukemia. *N Engl J Med*. 1986 Apr 24;314(17):1065-9.

Hehlmann R, Heimpel H, Hasford J, Kolb HJ, Pralle H, Hossfeld DK, Queisser W, Löffler H, Hochhaus A, Heinze B, et al. Randomized comparison of interferon-alpha with busulfan and hydroxyurea in chronic myelogenous leukemia. The German CML Study Group. *Blood*. 1994 Dec 15;84(12):4064-77.

Guilhot F, Chastang C, Michallet M, Guerci A, Harousseau JL, Maloisel F, Bouabdallah R, Guyotat D, Cheron N, Nicolini F, Abgrall JF, Tanzer J. Interferon alfa-2b combined with cytarabine versus interferon alone in chronic myelogenous leukemia. French Chronic Myeloid Leukemia Study Group. *N Engl J Med*. 1997 Jul 24;337(4):223-9.

Hughes TP, Kaeda J, Branford S, Rudzki Z, Hochhaus A, Hensley ML, Gathmann I, Bolton AE, van Hoomissen IC, Goldman JM, Radich JP; International Randomised Study of Interferon versus STI571 (IRIS) Study Group. Frequency of major molecular responses to imatinib or interferon alfa plus cytarabine in newly diagnosed chronic myeloid leukemia. *N Engl J Med*. 2003 Oct 9;349(15):1423-32.

Hochhaus A, Reiter A, Saussele S, Reichert A, Emig M, Kaeda J, Schultheis B, Berger U, Shepherd PC, Allan NC, Hehlmann R, Goldman JM, Cross NC. Molecular heterogeneity in complete cytogenetic responders after interferon-alpha therapy for chronic myelogenous leukemia: low levels of minimal residual disease are associated with continuing remission. German CML Study Group and the UK MRC CML Study Group. *Blood*. 2000 Jan 1;95(1):62-6.

Bonifazi F, de Vivo A, Rosti G, Guilhot F, Guilhot J, Trabacchi E, Hehlmann R, Hochhaus A, Shepherd PC, Steegmann JL, Kluin-Nelemans HC, Thaler J, Simonsson B, Louwagie A, Reiffers J, Mahon FX, Montefusco E, Alimena G, Hasford J, Richards S, Saglio G, Testoni N, Martinelli G, Tura S, Baccarani M; Europea Study Group on Interferon in Chronic Myeloid Leukemia; Italian Cooperative Study Group on CML; France Intergroup of CML; German CML Study Group; UK Medical Research Council Working Party on CML; Spanish CML Study Group; Australian CML Study Group; Swedish CML Study Group. Chronic myeloid leukemia and interferon-alpha: a study of complete cytogenetic responders. *Blood*. 2001 Nov 15;98(10):3074-81. Review.

Mahon FX, Delbrel X, Cony-Makhoul P, Fabères C, Boiron JM, Barthe C, Bilhou-Nabéra C, Pigneux A, Marit G, Reiffers J. Follow-up of complete cytogenetic remission in patients with

chronic myeloid leukemia after cessation of interferon alfa. *J Clin Oncol*. 2002 Jan 1;20(1):214-20.

Mauro MJ, Druker BJ, Maziarz RT. Divergent clinical outcome in two CML patients who discontinued imatinib therapy after achieving a molecular remission. *Leuk Res*. 2004 May;28 Suppl 1:S71-3.

Merante S, Orlandi E, Bernasconi P, Calatroni S, Boni M, Lazzarino M. Outcome of four patients with chronic myeloid leukemia after imatinib mesylate discontinuation. *Haematologica*. 2005 Jul;90(7):979-81.

Burchert A, Wöfl S, Schmidt M, Brendel C, Denecke B, Cai D, Odyvanova L, Lahaye T, Müller MC, Berg T, Gschaidmeier H, Wittig B, Hehlmann R, Hochhaus A, Neubauer A. Interferon-alpha, but not the ABL-kinase inhibitor imatinib (STI571), induces expression of myeloblastin and a specific T-cell response in chronic myeloid leukemia. *Blood*. 2003 Jan 1;101(1):259-64. Epub 2002 Jun 28.

Molldrem JJ, Lee PP, Wang C, Felio K, Kantarjian HM, Champlin RE, Davis MM. Evidence that specific T lymphocytes may participate in the elimination of chronic myelogenous leukemia. *Nat Med*. 2000 Sep;6(9):1018-23.

Molldrem JJ, Lee PP, Kant S, Wieder E, Jiang W, Lu S, Wang C, Davis MM. Chronic myelogenous leukemia shapes host immunity by selective deletion of high-avidity leukemia-specific T cells. *J Clin Invest*. 2003 Mar;111(5):639-47.

Kreutzman A, Rohon P, Faber E, Indrak K, Juvonen V, Kairisto V, Voglová J, Sinisalo M, Flochová E, Vakkila J, Arstila P, Porkka K, Mustjoki S. Chronic myeloid leukemia patients in prolonged remission following interferon- α monotherapy have distinct cytokine and oligoclonal lymphocyte profile. *PLoS One*. 2011;6(8):e23022. doi: 10.1371/journal.pone.0023022. Epub 2011 Aug 9.

Baccarani M, Martinelli G, Rosti G, Trabacchi E, Testoni N, Bassi S, Amabile M, Soverini S, Castagnetti F, Cilloni D, Izzo B, de Vivo A, Messa E, Bonifazi F, Poerio A, Luatti S, Giugliano E, Alberti D, Fincato G, Russo D, Pane F, Saglio G; GIMEMA Working Party on Chronic Myeloid Leukemia. Imatinib and pegylated human recombinant interferon-alpha2b in early chronic-phase chronic myeloid leukemia. *Blood*. 2004 Dec 15;104(13):4245-51. Epub 2004 Aug 19.

Preudhomme C, Guilhot J, Nicolini FE, Guerci-Bresler A, Rigal-Huguet F, Maloisel F, Coiteux V, Gardembas M, Berthou C, Vekhoff A, Rea D, Jourdan E, Allard C, Delmer A, Rousselot P, Legros L, Berger M, Corm S, Etienne G, Roche-Lestienne C, Eclache V, Mahon FX, Guilhot F; SPIRIT Investigators; France Intergroupe des Leucémies Myéloïdes Chroniques (Fi-LMC). Imatinib plus peginterferon alfa-2a in chronic myeloid leukemia. *N Engl J Med*. 2010 Dec 23;363(26):2511-21. doi: 10.1056/NEJMoa1004095.

Simonsson B, Gedde-Dahl T, Markevärn B, Remes K, Stentoft J, Almqvist A, Björemann M, Flogegård M, Koskenvesa P, Lindblom A, Malm C, Mustjoki S, Myhr-Eriksson K, Ohm L, Räsänen A, Sinisalo M, Själander A, Strömberg U, Bjerrum OW, Ehrencrona H, Gruber F, Kairisto V, Olsson K, Sandin F, Nagler A, Nielsen JL, Hjorth-Hansen H, Porkka K; Nordic CML Study Group. Combination of pegylated IFN- α 2b with imatinib increases molecular response rates in patients with low- or intermediate-risk chronic myeloid leukemia. *Blood*. 2011 Sep 22;118(12):3228-35. doi: 10.1182/blood-2011-02-336685. Epub 2011 Jun 17.

Hehlmann R, Lauseker M, Jung-Munkwitz S, Leitner A, Müller MC, Pletsch N, Proetel U, Haferlach C, Schlegelberger B, Balleisen L, Hänel M, Pffirmann M, Krause SW, Nerl C, Pralle H, Gratwohl A, Hossfeld DK, Hasford J, Hochhaus A, Saussele S. Tolerability-adapted imatinib 800 mg/d versus 400 mg/d versus 400 mg/d plus interferon- α in newly diagnosed chronic myeloid leukemia. *J Clin Oncol*. 2011 Apr 20;29(12):1634-42. doi: 10.1200/JCO.2010.32.0598. Epub 2011 Mar 21.

Nicolini FE, Etienne G, Dubruille V, Roy L, Huguet F, Legros L, Giraudier S, Coiteux V, Guerci-Bresler A, Lenain P, Cony-Makhoul P, Gardembas M, Hermet E, Rousselot P, Amé S, Gagnieu MC, Pivot C, Hayette S, Maguer-Satta V, Etienne M, Dulucq S, Rea D, Mahon FX. Nilotinib and peginterferon alfa-2a for newly diagnosed chronic-phase chronic myeloid leukaemia (NiloPeg): a multicentre, non-randomised, open-label phase 2 study. *Lancet Haematol*. 2015 Jan;2(1):e37-46. doi: 10.1016/S2352-3026(14)00027-1. Epub 2015 Jan 7.

Burchert A, Müller MC, Kostrewa P, Erben P, Bostel T, Liebler S, Hehlmann R, Neubauer A, Hochhaus A. Sustained molecular response with interferon alfa maintenance after induction therapy with imatinib plus interferon alfa in patients with chronic myeloid leukemia. *J Clin Oncol*. 2010 Mar 10;28(8):1429-35. doi: 10.1200/JCO.2009.25.5075. Epub 2010 Feb 8.

Burchert A, Saussele S, Eigendorff E, Müller MC, Sohlbach K, Inselmann S, Schütz C, Metzelder SK, Ziermann J, Kostrewa P, Hoffmann J, Hehlmann R, Neubauer A, Hochhaus A. Interferon alpha 2 maintenance therapy may enable high rates of treatment discontinuation in chronic myeloid leukemia. *Leukemia*. 2015 Jun;29(6):1331-5. doi: 10.1038/leu.2015.45. Epub 2015 Feb 25.

Baccarani M, Rosti G, de Vivo A, Bonifazi F, Russo D, Martinelli G, Testoni N, Amabile M, Fiacchini M, Montefusco E, Saglio G, Tura S; Italian Cooperative Study Group on Myeloid Leukemia. A randomized study of interferon-alpha versus interferon-alpha and low-dose arabinosyl cytosine in chronic myeloid leukemia. *Blood*. 2002 Mar 1;99(5):1527-35.

Lipton JH, Khoroshko N, Golenkov A, Abdulkadyrov K, Nair K, Raghunadharao D, Brummendorf T, Yoo K, Bergstrom B; Pegasys CML Study Group. Phase II, randomized, multicenter, comparative study of peginterferon-alpha-2a (40 kD) (Pegasys) versus interferon alpha-2a

[\(Roferon-A\) in patients with treatment-naïve, chronic-phase chronic myelogenous leukemia. *Leuk Lymphoma*. 2007 Mar;48\(3\):497-505.](#)

[Koskenvesa P, Kreutzman A, Rohon P, Pihlman M, Vakkila E, Räsänen A, Vapaatalo M, Remes K, Lundán T, Hjorth-Hansen H, Vakkila J, Simonsson B, Mustjoki S, Porkka K. Imatinib and pegylated IFN- \$\alpha\$ 2b discontinuation in first-line chronic myeloid leukemia patients following a major molecular response. *Eur J Haematol*. 2014;92\(5\):413-20. doi: 10.1111/ejh.12258. Epub 2014 Jan 28.](#)

[Faderl S, Talpaz M, Estrov Z, Kantarjian HM. Chronic myelogenous leukemia: biology and therapy. *Ann Intern Med*. 1999 Aug 3;131\(3\):207-19. Review.](#)

[Saußeule S, Richter J, Hochhaus A, Mahon FX. The concept of treatment-free remission in chronic myeloid leukemia. *Leukemia*. 2016 Aug;30\(8\):1638-47. doi: 10.1038/leu.2016.115. Epub 2016 May 2. Review.](#)

[Rea D, Nicolini FE, Tulliez M, Guilhot F, Guilhot J, Guerci-Bresler A, Gardembas M, Coiteux V, Guillerm G, Legros L, Etienne G, Pignon JM, Villemagne B, Escoffre-Barbe M, Ianotto JC, Charbonnier A, Johnson-Ansah H, Noel MP, Rouselot P, Mahon FX; France Intergroupe des Leucémies Myéloïdes Chroniques. Discontinuation of dasatinib or nilotinib in chronic myeloid leukemia: interim analysis of the STOP 2G-TKI study. *Blood*. 2017 Feb 16;129\(7\):846-854. doi: 10.1182/blood-2016-09-742205. Epub 2016 Dec 8.](#)

[Mahon, F., Richter, J., Guilhot, J., Muller, M. C., Dietz, C., Porkka, K., Hjorth-Hansen, H., Gruber, F., Panagiotidis, P., Ossenkoppele, G. J., Mayer, J., Almeida, A., Machova Polakova, K., Ehrencrona, H., Kairisto, V., Berger, M. G., Olsson Stromberg, U., Mustjoki, S., Hochhaus, A., Pfirrmann, M., & Saussele, S. \(2014\). Interim Analysis of a Pan European Stop Tyrosine Kinase Inhibitor Trial in Chronic Myeloid Leukemia : The EURO-SKI study. *Blood*, 124\(21\), 151. Accessed March 07, 2017. Retrieved from <http://www.bloodjournal.org/content/124/21/151>.](#)

[Kluin-Nelemans HC, Kester MG, van deCorput L, Boor PP, Landegent JE, van Dongen JJ, Willemze R, Falkenburg JH. Correction of abnormal T-cell receptor repertoire during interferon-alpha therapy in patients with hairy cell leukemia. *Blood*. 1998 Jun 1;91\(11\):4224-31.](#)

[Kantarjian HM, O'Brien S, Cortes JE, Shan J, Giles FJ, Rios MB, Faderl SH, Wierda WG, Ferrajoli A, Verstovsek S, Keating MJ, Freireich EJ, Talpaz M. Complete cytogenetic and molecular responses to interferon-alpha-based therapy for chronic myelogenous leukemia are associated with excellent long-term prognosis. *Cancer*. 2003 Feb 15;97\(4\):1033-41.](#)

[Hasford J, Baccarani M, Hoffmann V, Guilhot J, Saussele S, Rosti G, Guilhot F, Porkka K, Ossenkoppele G, Lindoerfer D, Simonsson B, Pfirrmann M, Hehlmann R. Predicting complete cytogenetic response and subsequent progression-free survival in 2060 patients with CML on](#)

imatinib treatment: the EUTOS score. *Blood*. 2011 Jul 21;118(3):686-92. doi: 10.1182/blood-2010-12-319038. Epub 2011 May 2.

Pfirschmann M, Lauseker M, Hoffmann VS, Hasford J. Prognostic scores for patients with chronic myeloid leukemia under particular consideration of competing causes of death. *Ann Hematol*. 2015 Apr;94 Suppl 2:S209-18. doi: 10.1007/s00277-015-2316-0. Epub 2015 Mar 27. Review.

Rasimas J, Katsounas A, Raza H, Murphy AA, Yang J, Lempicki RA, Osinusi A, Masur H, Polis M, Kottlilil S, Rosenstein D. Gene expression profiles predict emergence of psychiatric adverse events in HIV/HCV-coinfected patients on interferon-based HCV therapy. *J Acquir Immune Defic Syndr*. 2012 Jul 1;60(3):273-81. doi: 10.1097/QAI.0b013e31824c17c4. Erratum in: *J Acquir Immune Defic Syndr*. 2012 Aug 15;60(5):e122.

Sokal JE, Cox EB, Baccarani M, Tura S, Gomez GA, Robertson JE, Tso CY, Braun TJ, Clarkson BD, Cervantes F, et al. Prognostic discrimination in "good-risk" chronic granulocytic leukemia. *Blood*. 1984 Apr;63(4):789-99.

Hasford J, Pfirschmann M, Hehlmann R, Allan NC, Baccarani M, Kluijn-Nelemans JC, Alimena G, Steegmann JL, Ansari H. A new prognostic score for survival of patients with chronic myeloid leukemia treated with interferon alfa. Writing Committee for the Collaborative CML Prognostic Factors Project Group. *J Natl Cancer Inst*. 1998 Jun 3;90(11):850-8.

Pfirschmann M, Baccarani M, Saussele S, Guilhot J, Cervantes F, Ossenkoppele G, Hoffmann VS, Castagnetti F, Hasford J, Hehlmann R, Simonsson B. Prognosis of long-term survival considering disease-specific death in patients with chronic myeloid leukemia. *Leukemia*. 2016 Jan;30(1):48-56. doi: 10.1038/leu.2015.261. Epub 2015 Sep 29.

Tateno M, Honda M, Kawamura T, Honda H, Kaneko S. Expression profiling of peripheral-blood mononuclear cells from patients with chronic hepatitis C undergoing interferon therapy. *J Infect Dis*. 2007 Jan 15;195(2):255-67. Epub 2006 Dec 13.

Zimmerer JM, Lesinski GB, Ruppert AS, Radmacher MD, Noble C, Kendra K, Walker MJ, Carson WE 3rd. Gene expression profiling reveals similarities between the in vitro and in vivo responses of immune effector cells to IFN-alpha. *Clin Cancer Res*. 2008 Sep 15;14(18):5900-6. doi: 10.1158/1078-0432.CCR-08-0846.

Osinusi A, Rasimas JJ, Bishop R, Proschan M, McLaughlin M, Murphy A, Cortez KJ, Polis MA, Masur H, Rosenstein D, Kottlilil S. HIV/Hepatitis C virus-coinfected virologic responders to pegylated interferon and ribavirin therapy more frequently incur interferon-related adverse events than nonresponders do. *J Acquir Immune Defic Syndr*. 2010 Mar;53(3):357-63. doi: 10.1097/QAI.0b013e3181c7a29d.

[Hasham A, Zhang W, Lotay V, Haggerty S, Stefan M, Concepcion E, Dieterich DT, Tomer Y. Genetic analysis of interferon induced thyroiditis \(IIT\): evidence for a key role for MHC and apoptosis related genes and pathways. J Autoimmun. 2013 Aug;44:61-70. doi: 10.1016/j.jaut.2013.04.002. Epub 2013 May 15.](#)

[Pfirrmann M, Hochhaus A, Lauseker M, Saussele S, Hehlmann R, Hasford J. Recommendations to meet statistical challenges arising from endpoints beyond overall survival in clinical trials on chronic myeloid leukemia. Leukemia. 2011 Sep;25\(9\):1433-8. doi: 10.1038/leu.2011.116. Epub 2011 May 20.](#)

[Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med. 2007 May 20;26\(11\):2389-430.](#)

Responsible Party: Philipps University Marburg Medical Center

ClinicalTrials.gov Identifier: [NCT03117816](#) [History of Changes](#)

Other Study ID Numbers: KKS-227
2016-001030-94 (EudraCT Number)

First Submitted: March 8, 2017

First Posted: April 18, 2017

Last Update Posted: August 22, 2017

Last Verified: April 2017

Individual Participant Data (IPD) Sharing Statement:

Plan to Share IPD: No

Studies a U.S. FDA-regulated Drug Product: No

Studies a U.S. FDA-regulated Device Product: No

Keywords provided by Philipps University Marburg Medical Center:

deep molecular remission of MR4 or better

Additional relevant MeSH terms:

Leukemia	Interferons
Leukemia, Myeloid	Interferon-alpha
Leukemia, Myelogenous, Chronic, BCR-ABL Positive	Antineoplastic Agents
Neoplasms by Histologic Type	Antiviral Agents
Neoplasms	Anti-Infective Agents
Myeloproliferative Disorders	Immunologic Factors
	Physiological Effects of Drugs

Bone Marrow Diseases

Hematologic Diseases