EASY TO MISS

IMPOSSIBLE TO IGNORE
PNH: Progressive, destructive, life threatening—and vital to identify in high-risk populations.

IDENTIFY

- 35% of PNH patients die within 5 years of diagnosis, warranting early identification and intervention.
- PNH consensus guidelines recommend testing patients at high risk for PNH, including those patients who present with Coombs-negative hemolytic anemia, hemoglobinuria, aplastic anemia, refractory anemia-myelodysplastic syndromes, unexplained cytopenias, and unexplained thrombosis (venous or arterial).

DIAGNOSE

- Performing flow cytometry on peripheral blood is the gold standard diagnostic test for PNH; the Clinical Cytometry Society has recently provided guidelines for testing specific cell populations.
- PNH diagnosis is dependent on the deficiency of at least 2 GPI-linked antigens on more than 1 cell lineage (ie, granulocytes, monocytes, and erythrocytes).

MANAGE

- Ongoing patient assessments (including both flow cytometry and patient-reported signs and symptoms) are crucial for diagnosis and effective monitoring of PNH.
- PNH cell populations can increase rapidly and unpredictably over time.
- PNH consensus guidelines recommend continued monitoring of patients at high risk for PNH.

Learn more about identifying and evaluating high-risk patients for PNH with flow cytometry at PNHSource.com.

References:
How do you get double the exposure for the same price?

Your classified advertisement in *Blood* gives you more exposure than you think. When you place a print advertisement, you will also receive a free 30-day* posting on the American Society of Hematology’s online Job Bank. This employment resource is located at www.hematology.org and is free for all job seekers. For more information on submitting a classified ad in *Blood*, contact Valerie Marvin at vmarvin@cunnasso.com or at 201-767-4170.

*Your 30-day online posting will start when your print advertisement first appears in *Blood*. 

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**2011 ASPIRE Hemophilia Research Awards**

Pfizer is proud to announce the Advancing Science through Pfizer – Investigator Research Exchange (ASPIRE) 2011 Investigator Awards in Hemophilia Research, a competitive, peer-reviewed grants program sponsored by Pfizer for investigators in the United States.

**Mission**

- To support basic science, translational and clinical research through a competitive grants program that advances medical knowledge in the pathogenesis and treatment of hemophilia.
- To support academic research as well as the career development of promising young and established scientists.

**Area of Research Focus**

Pfizer will support competitive grant programs which address one of the following areas in Hemophilia A and/or Hemophilia B.

- Epidemiology / burden of disease / Outcomes Research
- Patient adherence to prescribed regimen
- Routine prophylaxis and preventative treatment
- Surgical prophylaxis, dosing
- On Demand dosing
- Treatment of inhibitors: Immune Tolerance Therapy, inhibitor bypass therapy
- Switching experience
- Management of adolescent Hemophilia patients & quality of life
- Management of the aging hemophilia population
- Basic science: Point of differentiation study
- Clinical monitoring of hemophilia treatment
- Recovery experience (hemophilia B patients)

**Application & Selection Process**

Application is open to US investigators. Selection of research proposals will be performed by an independent, external expert panel comprised of nationally known academic clinicians. Project duration should be 1-3 years and should be approximately $100,000/year, inclusive of overhead costs (capped at 28%).

For more information please visit [www.aspireresearch.org](http://www.aspireresearch.org)

The best way to fight cancer is to prevent it in the first place, and at UPMC Cancer Centers and the University of Pittsburgh Cancer Institute (UPCI), we are leading the charge. Our experts are nationally and internationally recognized for their work in identifying a wide scope of prevention strategies — from studying biomarkers in the blood to identify those at risk, to helping people to change personal risk behaviors, to establishing targeted interventions to block the effects of the environment in causing cancer, to developing promising vaccines to prevent disease recurrence — including the first trial to effectively activate a patient's own immune system to prevent the progression of premalignant disease. UPCI is western Pennsylvania's only NCI-designated Comprehensive Cancer Center. Our researchers work closely with oncologists at UPMC Cancer Centers, the nation's largest integrated cancer care network, to rapidly translate research into effective new strategies for the prevention, detection, and treatment of cancer. This means that more than 36,000 new patients each year are benefiting from the most advanced cancer therapies. To learn more about research and treatment at UPMC Cancer Centers and the University of Pittsburgh Cancer Institute, call 1-800-533-UPMC or visit UPMCPHysicianResources.com.

Affiliated with the University of Pittsburgh School of Medicine, UPMC is ranked among the nation's best hospitals by U.S. News & World Report. UPMC Cancer Centers works in tandem with the University of Pittsburgh Cancer Institute, a National Cancer Institute-designated Comprehensive Cancer Center.
Hematology Web Focus is a new publication designed for clinicians. This resource highlights article content published by prominent experts in the field and selects the articles that enhances the clinicians’ ability to effectively treat diseases.

The first focus topic, Multiple Myeloma, provides an overview and the most timely and relevant articles in the following areas:

- Asymptomatic Myeloma/MGUS
- Induction Therapy
- Transplantation
- Relapsed/Refractory Disease
- Complete Multiple Myeloma Reading List

Future topics will include Acute Lymphocytic Leukemia, Chronic Lymphocytic Leukemia, and Von Willebrand Disease

Free to ASH Members and Blood subscribers, visit www.hematologywebfocus.org for more information and to begin using this resource today. If you have any questions, please call 866-828-1231. International callers dial +1-202-776-0544.

Not an ASH Member or subscriber of Blood? Create an account for a free trial subscription to Hematology Web Focus at www.hematologywebfocus.org

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TREANDA® is his chemo.
This is his therapy.
TREANDA was evaluated in a single-arm pivotal study of 100 patients with indolent B-cell NHL that had progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen. Patients were scheduled to receive TREANDA 120 mg/m² on Days 1 and 2 of a 21-day treatment cycle, up to 8 cycles.

TREANDA was generally well tolerated in 2 single-arm studies of patients with indolent B-cell NHL that had progressed (N=176).

The most common non-hematologic adverse reactions (frequency ≥ 30%) were nausea (75%), fatigue (57%), vomiting (40%), diarrhea (37%), and pyrexia (34%) (N=176). The most common hematologic abnormalities (frequency ≥ 15%) were lymphopenia (99%), leukopenia (94%), anemia (88%), neutropenia (86%), and thrombocytopenia (86%).

TREANDA is indicated for the treatment of patients with indolent B-cell non-Hodgkin’s lymphoma (NHL) that has progressed during or within 6 months of treatment with rituximab or a rituximab-containing regimen.

**Selected Safety Information**

- Serious adverse reactions, including myelosuppression, infections, infusion reactions and anaphylaxis, tumor lysis syndrome, skin reactions including SJS/TEN, other malignancies, and extravasation, have been associated with TREANDA. Some reactions, such as myelosuppression, infections, and SJS/TEN (when TREANDA was administered concomitantly with allopurinol and other medications known to cause SJS/TEN), have been fatal. Patients should be monitored closely for these reactions and treated promptly if any occur.

- Adverse reactions may require interventions such as decreasing the dose of TREANDA, or withholding or delaying treatment. Myelosuppression is frequently severe and should be expected when treating patients with TREANDA.

- TREANDA is contraindicated in patients with a known hypersensitivity to bendamustine or mannitol. Women should be advised to avoid becoming pregnant while using TREANDA.

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**ORR**: **INDOLENT B-CELL NON-HODGKIN’S LYMPHOMA (NHL) THAT HAS PROGRESSED**

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*Overall response rate (ORR) was defined as a best response of a complete response (CR), unconfirmed complete response (CRu), or partial response (PR) during the study (ORR=CR+CRu+PR). Independent Review Committee assessment was based on modified International Working Group response criteria (IWG-RC). Modifications to IWG-RC specified that persistently positive bone marrow in patients who met all other criteria for CR would be scored as PR. Bone marrow sample lengths were not required to be ≥20 mm.

CI=confidence interval.

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INDICATIONS AND USAGE: Has Progressed

CONTRAINDICATIONS: Brief Summary of Prescribing Information for Indolent B-cell Non-Hodgkin’s Lymphoma That includes the following: myeloproliferative neoplasms, chronic myeloid leukemia, and bronchial carcinoma. The association with TREANDA therapy has not been ruled out. The intravenous LD50 of bendamustine HCl is 240 mg/m2 in the mouse and rat. Toxicities included sedation, tremor, ataxia, convulsions and respiratory distress. Across all clinical experience, the reported maximum single dose received was 280 mg/m2. Three of four patients treated with bendamustine developed ECG changes consistent with myocardial ischemia and or hypotension. The changes included QT prolongation (one patient), sinus tachycardia (one patient), ST and T wave changes (one patient), and left anterior hemiblock (one patient). The following serious adverse reactions have been associated with bendamustine and are considered serious adverse reactions. Some have occurred frequently in clinical trials, but their frequency cannot be determined. Where skin reactions occur, they may be progressive and increase in severity with extravasations, including monitoring of the intravenous infusion site for redness, swelling, pain, infection, and necrosis during and after administration of TREANDA. Use in Pregnancy. The following adverse drug reactions have been identified during post-marketing experience:

Vascular disorders, All Grades and Grade 3/4—Hypotension: 10 (6), 2 (1)

Percent of patients

Hematologic Variable

- Anemia (99%); 4 (5), 1 (1)
- Hemoglobin Decreased 88 11
- Neutrophils Decreased 86 60
- Platelets Decreased

Table 4: Incidence of Hematology Laboratory Abnormalities in Patients Who Received TREANDA in the NHL Studies

Percent of patients

45; hematologic toxicity: for Grade 4 toxicity, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modifications for non-hematologic toxicity: for Grade 4 toxicity, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modification for intravenous infusion reactions: if Grade 4 toxicity recurs, the dose to reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle for Grade 4 toxicity. If Grade 3 or greater toxicity occurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modification for myelosuppression: if Grade 4 toxicity occurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modification for pulmonary toxicity: if Grade 4 toxicity occurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modification for infection: if Grade 4 toxicity occurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modification for neutropenia: if Grade 4 toxicity occurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modification for anemia: if Grade 4 toxicity occurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modification for neutropenia: if Grade 4 toxicity occurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modification for anemia: if Grade 4 toxicity occurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modification for neutropenia: if Grade 4 toxicity occurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modification for anemia: if Grade 4 toxicity occurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modification for neutropenia: if Grade 4 toxicity occurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle. Dose modification for anemia: if Grade 4 toxicity occurs, reduce the dose to 60 mg/m^2 on Days 1 and 2 of each cycle.
Blood, the Journal of the American Society of Hematology, published online and in print, provides an international forum for the publication of original articles describing basic laboratory, translational, and clinical investigations in hematology. Acceptance of manuscripts is based on the originality and importance of the observations or investigations, the quality of the work and validity of the evidence, the clarity of presentation, and the relevance to our readership and field. Membership in the American Society of Hematology is not required for submission. All articles are expected to be concise, well organized and clearly written. Authors submit a manuscript with the understanding that the manuscript (or its essential substance) has not been published other than as an abstract in any language or format and is not currently submitted elsewhere for print or electronic publication.

Blood receives over 5,000 online submissions per year and accepts about 25% of them after a thorough and impartial peer review. Accepted papers are published ahead of print as First Edition papers. The average time to first decision is 21.3 days. The average time from acceptance to publication is 7 weeks. Non-English-speaking authors are encouraged to visit the Authors Guide online at http://bloodjournal.hematologylibrary.org/authors/authorguide.dtl to view links to professional editing services that may help improve the presentation of the paper.

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Authors are invited to contact the Editor-in-Chief (bloodeditor@hematology.org) prior to submission if they are uncertain whether their work falls within the general scope. Immunobiology encompasses a wide spectrum of research, but Blood can accommodate only papers that have clear and important implications for hematology. Preference is given to papers focusing on human immunobiology and which have significant implications for understanding of normal or malignant hematologic processes. Papers on tumor immunology and tumor vaccine development may be appropriate if the target cells are hematologic malignancies, but Blood can no longer accommodate tumor immunology papers that focus solely on nonhematologic tumor models. Papers focusing on autoimmunity and utilizing nonhematologic models are not within the scope of Blood. Papers on the immune response to specific microbiologic pathogens are also generally outside the scope of Blood, except those focusing on the direct links of Epstein-Barr virus, hepatitis virus, or HTLV to hematologic malignancies. These and other papers felt to be outside the scope of Blood and more appropriate for an immunology, infectious diseases, or tumor immunology Journal will be returned to the author without full peer review.

Regular Articles. Maximum length for a Regular Article is 5,000 words of text, not counting the abstract, tables, figure legends, and references; abstracts must not exceed 200 words and should be constructed as a single narrative paragraph with no subheadings or references. Submissions are limited to a total of 7 figures and digital images are required. There is no limit on the number of tables. References should be limited to 50. The sections of a Regular Article should be ordered Abstract, Introduction, Methods, Results, Discussion, Acknowledgments, Authorship Contributions and Disclosure of Conflicts of Interest, References, Tables, Figure Legends, and Figures. Supplemental files to be published online-only may include additional information regarding methodology, supplemental figures or tables, or primary data sets. Any involvement of medical writers/researchers, particularly those employed or supported by the pharmaceutical industry, in the writing of an article must be clearly defined and disclosed in the Authorship and/or the Acknowledgments section as appropriate. This type of involvement must also be disclosed to the Editor-in-Chief in the cover letter. Definitive original research articles of exceptional scientific importance may be considered for designation as Plenary Papers. The decision to highlight an article as a Plenary Paper rests entirely with the Editors.

Brief Reports. Short manuscripts definitively documenting either experimental results or informative clinical observations will be considered for publication in this category. Single-case reports or case series can almost never be accommodated, unless they elucidate novel and important disease biology or approaches to therapy. Brief Reports are not intended to allow publication of incomplete or preliminary findings. The review process is equally rigorous as for Regular Articles and the acceptance rate is lower. Brief Reports may not exceed 1,200 words of text not counting the abstract, figure legends, and references; abstracts must not exceed 150 words and should be a single paragraph with no subheadings. Only 2 figures/tables and 25 references may be included. The sections of a Brief Report should be ordered Abstract, Introduction, Methods sufficiently informative to allow reproduction of the data, followed by a combined Results and Discussion section, Acknowledgments, Authorship Contributions and Disclosure of Conflicts of Interest, References, Tables, Figure Legends, and Figures.

e-Blood, e-Blood is a new manuscript category for publication of very well designed systems biology work (e.g., genomics, proteomics etc.) that is largely descriptive. Such work will be published as an online-only paper if utilization of the data by others will significantly advance the field. e-Blood articles will be fully citable, and will represent genuine Blood publication. They will undergo standard rigorous peer review if deemed potentially appropriate for publication by Blood Editors. Accepted e-Blood articles will be published in First Edition and then copyedited and composed identical to other Blood papers, but will not be included in a print edition of the Journal, although they will be listed in a printed Table of Contents when their final typeset version is available online. Papers may be submitted by authors directly for consideration as e-Blood articles, or may be recommended by Editors for publication as an e-Blood article after being considered for publication as a Regular Article, if deemed more appropriate for the e-Blood article type. The maximum length for an
e-Blood article is 5,000 words of text, not counting the abstract, tables, figure legends, and references; abstracts must not exceed 200 words and should be a single paragraph with no subheadings. Digital images are mandatory. References should be limited to 50. Primary data must be deposited in a public repository. The sections of an e-Blood article should be ordered Abstract, Introduction, Methods, Results, Discussion, References, Acknowledgments, Authorship Contributions, Disclosure of Conflicts of Interest, References, Tables, Figure Legends, and Figures. Review Articles. Review Articles are welcomed by the Journal and are generally solicited by the Editor-in-Chief; however, authors wishing to submit an unsolicited Review Article are invited to contact the Editor-in-Chief prior to submission, in order to screen the proposed topic for relevance and priority, given other Review Articles that may already be in preparation. Review Articles should focus on recent scientific or clinical advances in an area of broad interest to those in the field of hematology. Such articles must be concise and critical and should include appropriate references to the literature. All Review Articles, even those solicited by the Editors, are rigorously peer reviewed before a final publication decision is made. Review Articles should not exceed 5,000 words in length, must include an abstract of 200 words or fewer, and may not have more than 100 references. The use of tables and color figures to summarize critical points is encouraged; the Journal offers assistance with preparation or improvement of figures by professional illustrators, once the article is accepted. Any involvement of medical writers/researchers, particularly those employed or supported by the pharmaceutical industry, in the writing of a Review Article must be clearly defined and disclosed in the Authorship section. For Review Articles, this type of involvement must be discussed with the Editor-in-Chief before the submission of the article. Generally, involvement of medical writers/researchers supported by the pharmaceutical industry is not acceptable for Review Articles published in Blood. How I Treat. The Journal welcomes articles written by expert clinicians offering up-to-date information and guidance regarding diagnosis and treatment of hematological diseases and clinical situations. Clear distinctions should be made between evidence-based versus experience-based recommendations. The pieces can be constructed as a standard narrative or be structured around a case or cases illustrating specific clinical situations. These pieces are generally solicited by the Editor-in-Chief, but any interested author is invited to correspond with the Editor-in-Chief prior to submission to discuss the suitability of the proposed subject matter. The length should not exceed 5,000 words; the abstract must not exceed 200 words; and references are limited to 100. Any involvement of medical writers/researchers, particularly those employed or supported by the pharmaceutical industry, in the writing of an article must be clearly defined and disclosed in the Authorship section. For How I Treat articles, this type of involvement must be discussed with the Editor-in-Chief before the submission of the article. Generally, involvement of medical writers/researchers supported by the pharmaceutical industry is not acceptable for How I Treat articles published in Blood. Perspectives. Perspectives are articles discussing significant topics and controversies relevant to hematology, generally from a more personal or opinion-based standpoint than a Review Article. Interested authors should correspond with the Editor-in-Chief prior to submission to discuss the suitability of the proposed subject matter. The length should not exceed 5,000 words; the abstract must not exceed 200 words; and references are limited to 100. Typically, Perspectives should state the topic and background information concisely, discuss opposing viewpoints, and make recommendations for further investigations or actions. Inside Blood. The Editors invite experts in the field to write brief commentaries introducing and placing into context several selected primary research articles included in each issue of Blood. Plenary Papers. Definitive original research articles of exceptional scientific importance may be considered for designation as Plenary Papers. The decision to highlight an article as a Plenary Paper rests entirely with the Editors. Data Supplements. The Journal encourages the submission of Data Supplements linked to primary research articles, including videos and short movies, that enhance the understanding of the science discussed in the manuscript. 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If your submission is accepted, your figure(s) will also be submitted for consideration to the ASH Image Bank. All other policies governing submissions to the Journal also apply to Blood Work. There will be no submission fee and no color figure charges for publication if accepted. Letters to the Editor. Constructive comments on published articles or on current topics in hematology are welcome and will be published if appropriate and based on priority and interest to readership. Letters should include no more than 500 words of text, 5–10 references, and 1 figure or table. No abstract is required, but please include a brief title. Submission fees and page charges do not apply to Letters. Letters are screened by the Editor-in-Chief and, if deemed appropriate and relevant, may also be peer reviewed and/or accompanied by a Response from the authors of the initial article. Public Access. 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THE ONLY HYPOMETHYLATING AGENT APPROVED FOR 5-DAY DOSING

DACOGEN provides 2 dose options for your patients with myelodysplastic syndromes (MDS). ¹

- 20 mg/m² by IV over 1 hour repeated daily for 5 days. Repeat cycle every 4 weeks
- 15 mg/m² by IV over 3 hours repeated every 8 hours for 3 days. Repeat cycle every 6 weeks
- With either regimen, it is recommended that the patient be treated for a minimum of 4 cycles. However, a complete or partial response may take longer than 4 cycles

See Important Safety Information below and the Dosage and Administration section of the full Prescribing Information.

DACOGEN is indicated for the treatment of patients with MDS including those who are:

- Previously treated and untreated
- De novo and secondary
  - All FAB subtypes (RA, RARS, RAEB, RAEB-t, CMML)
  - Intermediate-1, Intermediate-2, High-Risk International Prognostic Scoring System groups

Important Safety Information

Treatment with DACOGEN is associated with neutropenia and thrombocytopenia. Complete blood and platelet counts should be performed as needed to monitor response and toxicity but at a minimum prior to each dosing cycle. After administration of the recommended dosage for the first cycle, treatment for subsequent cycles should be adjusted if indicated by dose adjustment guidelines. Clinicians should consider the need for early institution of growth factors and/or antimicrobial agents for the prevention or treatment of infections in patients with MDS.

DACOGEN may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with DACOGEN and for 1 month following completion of treatment. Women of childbearing potential should be counseled to use effective contraception during this time. Men should be advised not to father a child while receiving treatment with DACOGEN and for 2 months following completion of treatment. DACOGEN may cause fetal harm. Men with female partners of childbearing potential should use effective contraception during this time.

In the phase 3 clinical trial, the highest incidence of Grade 3 or Grade 4 adverse events in the DACOGEN arm was neutropenia (87%), thrombocytopenia (85%), febrile neutropenia (23%), and leukopenia (22%). Bone marrow suppression was the most frequent cause of dose reduction, delay, and discontinuation. Six patients had fatal events associated with their underlying disease and myelosuppression (anemia, neutropenia, and thrombocytopenia) that were considered at least possibly related to drug treatment. Of the 83 DACOGEN-treated patients, 8 permanently discontinued therapy for adverse events compared to 1 of 81 patients in the supportive care arm.

In the single-arm study, the highest incidence of Grade 3 or Grade 4 adverse events was neutropenia (37%), thrombocytopenia (24%), and anemia (22%). Seventy-eight percent of patients had dose delays, the median duration of this delay was 7 days. Hematologic toxicities and infections were the most frequent causes of dose delays and discontinuation. Eight patients had fatal events due to infection and/or bleeding that were considered at least possibly related to drug treatment. Nineteen of 99 patients permanently discontinued therapy for adverse events.

Other commonly occurring reactions include fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhea, and hyperglycemia.

If hematologic recovery from a previous DACOGEN treatment cycle requires more than 6 weeks when administering the 3-day dosing, then the next DACOGEN cycle should be delayed and dosing temporarily reduced. When administering the 5-day dosing, the DACOGEN cycle should be delayed until there is hematologic recovery. If the following nonhematologic toxicities are present, DACOGEN treatment should not be restarted until the toxicity is resolved: (1) serum creatinine ≥2 mg/dl; (2) SGPT, total bilirubin ≥2 × ULN; and (3) active or uncontrolled infection.

Because there are no data on use of DACOGEN in patients with renal or hepatic dysfunction, DACOGEN should be used with caution in these patients.

Please see the accompanying brief summary of full Prescribing Information on the following page.

Reference: 1. Dacogen (decitabine) for Injection full prescribing information.
In the controlled trial using Dacogen dosed at 15 mg/m², administered by continuous intravenous infusion over 3 hours repeated every 8 hours for 7 weeks, decitabine did not affect survival, body weight gain or hematological measures.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving Dacogen and for 1 month following completion of treatment (seeDave [Anticancer Agents]). Appropriate contraceptive measures should be recommended for the duration of treatment. If a woman should become pregnant while receiving Dacogen, the pregnancy should be terminated. Decitabine is not expected to be present in breast milk. The effects of decitabine on nursing infants are unknown.

In vitro toxicity was observed. No live fetuses were seen at any dose when decitabine was injected on gestation day 9. A significant decrease in fetal body weight was observed when decitabine was injected on gestation day 10. Decitabine treatment of mice on gestation day 10 produced a significant decrease in fetal body weight and an increase in spontaneous abortions. A significant decrease in fetal body weight was observed when decitabine was injected on gestation day 11. Decitabine treatment of mice on gestation day 11 produced a significant decrease in fetal body weight and an increase in spontaneous abortions.

In conclusion, decitabine induced a significant decrease in fetal body weight and an increase in spontaneous abortions in mice. These findings suggest that decitabine is teratogenic in mice. However, the relevance of these findings to humans is uncertain. It is not known whether decitabine or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

In clinical trials with decitabine, anemia was the most common hematological side effect, occurring in at least 50% of patients. Neutropenia and thrombocytopenia were reported in at least 20% of patients. In a single-arm study (N=99) when Dacogen was dosed at 20 mg/m² intravenous, infused over one hour daily for 5 consecutive days, the highest incidence of Grade 3 or 4 adverse events in the Dacogen arm were neutropenia (87%), thrombocytopenia (85%), febrile neutropenia (61%) and anemia (29%). Seven patients had Grade 4 adverse events, of which one patient had Grade 4 neutropenia. Eight patients had Grade 3 adverse events, of which one patient had Grade 3 neutropenia. The most common nonhematological adverse events were nausea (37%), vomiting (28%), dyspepsia (28%), and diarrhea (27%). The following Adverse Events were reported in ≥ 5% of Patients in the Dacogen Group and at a Rate Greater than or Equal to the Control Group:

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**Blood and lymphatic system disorders**—Pancytopenia 5 (5%); Thrombocytosis 5 (5%); Thrombocytopenia 27 (27%); Neutropenia 12 (12%); Transfusion 19 (19%); Hemorrhage 10 (10%).  **Blood and lymphatic system disorders**—Pancytopenia 5 (5%); Thrombocytosis 5 (5%); Thrombocytopenia 27 (27%); Neutropenia 12 (12%); Transfusion 19 (19%); Hemorrhage 10 (10%).

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**Dermatologic disorders**—Hair color alteration 3 (3%).  **Dermatologic disorders**—Hair color alteration 3 (3%).

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**Gastrointestinal disorders**—Nausea 15 (15%).  **Gastrointestinal disorders**—Nausea 15 (15%).

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**Neoplastic and lymphoid tissue disorders**—Secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and International 1, International 2, and high-risk MDS subtypes.

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**Psychiatric disorders**—Psychosis 3 (3%).  **Psychiatric disorders**—Psychosis 3 (3%).

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**Respiratory, thoracic and mediastinal disorders**—Pneumonia NOS 18 (22), 11 (14); Cellulitis 10 (12), 6 (7); Candidal infection 2 (2), 1 (1); Respiratory failure 5 (6), 3 (4); Pulmonary edema NOS 5(6),0(0); Vision blurred 5(6),0(0).

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**Skin and appendage disorders**—Diabetes mellitus 11 (13%), 4 (5%); Paresthesia 17 (21%), 10 (13%); Exfoliative dermatitis 5 (6%), 2 (2%); Necrotic dermatitis 5 (6%), 2 (2%).

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**Systemic disorder**—Fatigue 14 (17%), 9 (11%); Fever 10 (12%), 7 (9%).

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**Vascular disorders**—Pulmonary embolism 4 (5%), 0 (0%); Pneumonia NOS 18 (22), 11 (14); Cellulitis 10 (12), 6 (7); Candidal infection 2 (2), 1 (1); Respiratory failure 5 (6), 3 (4); Pulmonary edema NOS 5(6),0(0); Vision blurred 5(6),0(0).

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**Hematologic toxicities and infections**—Hematologic toxicities and infections were the most frequent causes of dose delays and discontinuation. Eight patients had fatal events related to hematologic toxicities. Six patients had fatal events related to infection. One patient had fatal events related to both hematologic toxicities and infection.

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**Infections and infestations**—Bacterial infections were the most frequent cause of dose delays and discontinuation. Eight patients had fatal events related to bacterial infections. Six patients had fatal events related to infection. One patient had fatal events related to both bacterial infections and infection.

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**Liver chemistries and serum creatinine**—Liver chemistries and serum creatinine should be obtained prior to initiation of treatment. Complete blood counts and platelet counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each cycle. Liver chemistries and serum creatinine should be obtained prior to initiation of treatment. Complete blood counts and platelet counts should be performed as needed to monitor response and toxicity, but at a minimum, prior to each cycle.
Introducing our New Web 2.0 platform

We are very excited to announce the launch of our new Web 2.0 platform through our e-Publishing partner HighWire Press. The 2.0 infrastructure is designed to cooperate with emerging Web services and technologies, keeping Blood ahead of the technology curve.

We want to enhance your online experience and made this upgrade with our subscribers in mind. With 2.0, Blood will have new features that allow readers easier access to data more quickly. These interface features include:

- **Abstract preview**: Mouse-over pop-up abstract preview when the tables of contents or search results pages are on screen — no need to leave the page.
- **Tag-along navigation**: The navigation box follows alongside as the reader scrolls down the article page.
- **Feature hideaway**: Author affiliations, related links, and other article enhancements can be expanded or hidden.
- **Related articles search**: One-click search for related articles by author, keyword, or subject classification - from within an article.
- **Quick scan**: Content easily flows from the title and abstract to previous/next article links, allowing users to quickly scan the content.

We hope you enjoy this upgrade, and we will continue to look at technology and other ways we can provide *Blood* to you.
Dysregulated JAK signaling—a common link among MF, PV and ET

Excess cytokines may continuously activate receptors

MPL may be mutated and constitutively active

JAK2 may be mutated and constitutively active

Increased JAK1 signaling

Excess JAK activity leads to overactivation of STATs

Multiple abnormalities can lead to dysregulated JAK signaling

Janus kinase (JAK) pathway signaling is essential for normal hematopoiesis and immune function. JAK pathway dysregulation, however, leads to the development of 3 Philadelphia chromosome–negative myeloproliferative neoplasms (MPNs): myelofibrosis (MF), polycythemia vera (PV) and essential thrombocythemia (ET). Excessive JAK1 and JAK2 signaling overstimulates signal transducers and activators of transcription (STATs), which activate cell proliferation, survival of malignant cells and increased cytokine production. Manifestations of overactive signaling in MPNs include splenomegaly and constitutional symptoms.

Multiple abnormalities may cause JAK pathway dysregulation, including:

- **JAK2 mutations** — leading to constitutive activation of JAK2 and increased cell proliferation and survival of malignant cells. JAK2V617F is the most common mutation and results in a constitutively active form of the JAK2 protein.
- **Increased JAK1 signaling** — associated with increased cell proliferation and constitutional symptoms.
- **Excess cytokines** — leading to overactivation of the JAK signaling pathway and constitutional symptoms.
- **MPL mutations** — leading to constitutive JAK2 signaling and increased megakaryocyte production.

JAK dysregulation is thought to occur in most MPN patients, independent of JAK2V617F mutational status. In fact, many MF and ET patients do not have a known mutation. MF patients also have elevated levels of activated JAK1, which suggests that dysregulated JAK1 and JAK2 signaling is central to the pathogenesis of MF. Regardless of the mechanism of JAK dysregulation, further research on JAK1 and JAK2 mechanisms is providing new insight into their role in MPNs.

Visit www.MPNConnect.org/JAKs

To learn more about the dysregulated JAK pathway, visit MPNConnect.org/JAKs today and download the JAK Signaling in MPNs video. Other benefits include free educational resources such as an MPN presentation and brochure.
We’ll stop at

Introducing The Path in CML
More than just a research initiative... a mission
2011 ASH State-of-the-Art Symposium

SEPTEMBER 23-24, 2011 • CHICAGO, IL • PALMER HOUSE HILTON
At Bayer, scientific innovation in hemophilia has a simple mission: Help people live the lives they choose. Which is why we’re excited about potential treatments currently in development. Look to us for innovative research and see what opportunities develop in your patients’ lives.

BAYER—HEMOPHILIA CARE
Never losing sight of the human factor

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Translational Research Training in Hematology (TRTH) is a year-long training and mentoring program for early-career scientists interested in translational research in hematology. TRTH provides training to postdoctoral medical and biomedical and pharmaceutical translational scientists in pathogenesis, diagnostics and experimental treatments of hematological disorders.

About TRTH
TRTH is a joint effort of the European Hematology Association (EHA) and the American Society of Hematology (ASH) in response to the demand for translational research in Europe and the United States. The program hosts 20 promising young scientists for an intensive training course and two follow-up meetings over the span of one year.

Translational research
Laboratory-based translational research is the focus of TRTH. Training in biostatistics and biomarkers, genetics and molecular biology, ethics, and phase I clinical design is offered, along with practical advice on professional networking to help trainees build their careers in hematological translational research.

How to apply
Applicant research projects must be hypothesis-driven and directly connected to some aspect of human biology. Applicants must be members of either EHA or ASH.

• Step 1: A letter of intent (LOI), curriculum vitae (CV) and research project abstract must be submitted by May 1, 2011. A template LOI is available on the EHA website. Those who are eligible will be invited to proceed to step 2 and submit a full application.
• Step 2: Eligible candidates invited to submit a full application must submit a comprehensive hematological translational research project proposal and other required documents by September 1, 2011.

Important dates
Letter Of Intent due: May 1, 2011
Full application due: September 1, 2011

For more information
Contact the EHA Executive Office at training@ehaweb.org or +31 (0)70 3020 099

TRTH is being made possible by a generous unrestricted educational grant from the Wallace H. Coulter Foundation.
2011 ASH State-of-the-Art Symposium

SEPTEMBER 23-24, 2011 • CHICAGO, IL • PALMER HOUSE HILTON
Nplate® (romiplostim)  
Brief Summary

WARNINGS AND PRECAUTIONS

Bone Marrow Reticulin Formation and Risk for Bone Marrow Fibrosis

Nplate® administration increases the risk for development or progression of marrow reticulin deposition within the bone marrow. In clinical studies, Nplate® was discontinued in four of the 271 patients because of bone marrow reticulin deposition. Six additional patients had marrow reticulin deposition upon bone marrow biopsy. All 10 patients with bone marrow reticulin deposition had Nplate® doses ≥ 5 mcg/kg and six received doses ≥ 10 mcg/kg.

Progression to marrow fibrosis with cytopsins was not reported in the current study; one patient with ITP and hemolytic anemia developed marrow fibrosis with collagen during Nplate® therapy. Clinical studies have not included a risk of bone marrow fibrosis and worsening of cytopsins. Prior to institution of Nplate®, examine the peripheral blood smear closely to establish a baseline level of cellular morphologic abnormalities. Following identification of a stable Nplate® dose, examine peripheral blood smears and CBCs monthly for new or worsening morphologic abnormalities (eg, teardrop and nucleated red blood cells, immature white blood cells) or cytopsins. If the patient develops new or worsening morphologic abnormalities or cytopsins, discontinue treatment with Nplate® and consider a bone marrow biopsy, including staining for fibrosis [see Adverse Reactions (6.1)].

Worsened Thrombocytopenia After Cessation of Nplate®

Discontinuation of Nplate® may result in thrombocytopenia of greater severity compared to pre-Nplate® therapy. This worsened thrombocytopenia may increase the patient’s risk of bleeding, particularly if Nplate® is discontinued while the patient is on anti-coagulants or anti-fibrinolytic agents. In clinical studies of patients with chronic ITP who had Nplate® discontinued, four of 57 patients developed thrombocytopenia of greater severity than was present prior to Nplate® therapy. This worsened thrombocytopenia resolved within 14 days. Review the Nplate® NEXUS Program, obtain weekly CBCs, including platelet counts, for at least 2 weeks and consider alternative treatments for worsening thrombocytopenia, according to current treatment guidelines [see Adverse Reactions (6.1)].

Thrombotic/Thromboembolic Complications

Thrombotic/thromboembolic complications may result from excess increases in platelet counts. Excessive doses of Nplate® or median platelet counts in excess of 1000 x 10^9/L may increase the risk for thrombotic/thromboembolic complications. In controlled clinical studies, the incidence of thrombotic/thromboembolic complications was similar between patients treated with Nplate® and placebo. To minimize the risk for thrombotic/thromboembolic complications, do not use Nplate® in an attempt to normalize platelet counts. Follow the dose adjustment guidelines to achieve a platelet count of ≥ 50 x 10^9/L [see Dosage and Administration (2.1)].

Lack of Loss of Response to Nplate®

Hyporesponsiveness or failure to maintain a platelet response with Nplate® should prompt a search for causative factors, including neutralizing antibodies against Nplate® therapy. This worsened thrombocytopenia may increase the patient’s risk of bleeding, particularly if Nplate® is discontinued while the patient is on anti-coagulants or anti-fibrinolytic agents. In clinical studies of patients with chronic ITP who had Nplate® discontinued, four of 57 patients developed thrombocytopenia of greater severity than was present prior to Nplate® therapy. This worsened thrombocytopenia resolved within 14 days. Review the Nplate® NEXUS Program, obtain weekly CBCs, including platelet counts, for at least 2 weeks and consider alternative treatments for worsening thrombocytopenia, according to current treatment guidelines [see Adverse Reactions (6.1)].

Table 2. Adverse Drug Reactions Identified in the placebo-controlled Studies

<table>
<thead>
<tr>
<th>Preferred Term</th>
<th>Nplate® (n=84)</th>
<th>Placebo (n=41)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthralgia</td>
<td>25%</td>
<td>20%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>17%</td>
<td>9%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>16%</td>
<td>7%</td>
</tr>
<tr>
<td>Myalgia</td>
<td>14%</td>
<td>2%</td>
</tr>
<tr>
<td>Pain in Extremity</td>
<td>13%</td>
<td>5%</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>11%</td>
<td>0%</td>
</tr>
<tr>
<td>Shoulder Pain</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>7%</td>
<td>0%</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6%</td>
<td>0%</td>
</tr>
</tbody>
</table>

Among 142 patients with chronic ITP who received Nplate® in the single-arm extension study, the incidence rates of the adverse reactions occurred in a pattern similar to those reported in the placebo-controlled clinical studies.

Immunogenicity

As with all therapeutic proteins, patients may develop antibodies to the therapeutic protein. All patients were screened for immunogenicity to romiplostim using a BACore-based biosensor immunoassay. This assay is capable of detecting both high- and low-affinity binding antibodies that bind to romiplostim and cross-react with TPO. The samples from patients that tested positive for binding antibodies were further evaluated for neutralizing capacity using a cell-based bioassay.

In clinical studies, the incidence of preexisting antibodies to romiplostim was 8% (17/225) and the incidence of binding antibody development to romiplostim within the endogenous TPO during Nplate® treatment was 5% (12/225). Of the patients with positive antibodies to romiplostim or to TPO, one (0.4%) patient had neutralizing activity to romiplostim and none had neutralizing activity to TPO. No correlation was observed between antibody activity and clinical effectiveness or safety. Immunogenicity assay results are highly dependent on the sensitivity and specificity of the assay used in detection and may be influenced by several factors, including sample handling, storage conditions, and underlying disease. For these reasons, comparison of incidence of antibodies to romiplostim with the incidence of antibodies to other products may be misleading.

Drug Interactions

No formal drug interaction studies of Nplate® have been performed.

Use in Specific Populations

Pregnancy

Category C

There are no adequate and well-controlled studies of Nplate® use in pregnant women. In animal reproduction studies, embryofetal toxicity studies, romiplostim crossed the placenta, and adverse fetal effects included thrombocytopenia, postimplantation loss, and an increase in pup mortality. Nplate® should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

Pregnancy Registry: A pregnancy registry has been established to collect information about the effects of Nplate® use during pregnancy. Physicians are encouraged to register pregnant patients, or pregnant women may enroll themselves in the Nplate® pregnancy registry by calling 1-877-Nplate1 (1-877-675-2831). In rabbit and rat developmental toxicity studies, no evidence of fetal harm was observed at doses up to 100 and 50 mg/kg (42 and 212 times the human dose) and 10 and 5 mg/kg (32 and 158 times the human dose), respectively, based on body weight and postpartum growth retardation. In a prenatal and postnatal development study in rats, at doses 11 times the MHD, there was an increase in perinatal pup mortality. Romiplostim crossed the placental barrier in rats and increased fetal platelet counts at clinically equivalent and higher doses.

Nursing Mothers

It is not known whether Nplate® is excreted in human milk; however, human IgG is excreted in human milk. Published data suggest that breast milk antibodies do not enter neonatal and infant circulation in substantial amounts. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue Nplate®, taking into account the importance of Nplate® to the mother and the known benefits of nursing.

Pediatric Use

The safety and effectiveness in pediatric patients (< 18 years) have not been established.

Geriatric Use

Of the 271 patients who received Nplate® in ITP clinical studies, 55 (20%) were age 65 and over, and 27 (10%) were 75 and over. No overall differences in safety or efficacy have been observed between older and younger patients in the placebo-controlled studies, but greater sensitivity to adverse events in older patients cannot be ruled out. In general, dose adjustment for an elderly patient should be cautious, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Renal Impairment

No clinical studies were conducted in patients with renal impairment. Use Nplate® with caution in this population.

Hepatic Impairment

No clinical studies were conducted in patients with hepatic impairment. Use Nplate® with caution in this population.

OVERDOSAGE

In the event of overdose, platelet counts may increase excessively and result in thrombotic/thromboembolic complications. In this case, discontinue Nplate® and monitor platelet counts. Reinitiate treatment with Nplate® in accordance with dosing and administration recommendations [see Dosage and Administration (2.2)].

Rx Only. This brief summary is based on Nplate® prescribing information v. 1

Manufactured by: Amgen Inc.
One Amgen Center Drive
Thousand Oaks, California 91320-1799

This product, its production, and/or its use may be covered by one or more U.S. Patents, including U.S. Patent Nos. 6,355,809 and 7,189,827, as well as other patents or patents pending.

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Nplate® is indicated for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy. Nplate® should be used only in patients with ITP whose degree of thrombocytopenia and clinical condition increases the risk for bleeding. Nplate® should not be used in an attempt to normalize platelet counts.

IMPORTANT SAFETY INFORMATION

■ Serious adverse reactions associated with Nplate® in clinical studies were bone marrow reticulin deposition and worsening thrombocytopenia after Nplate® discontinuation. Additional risks include Bone Marrow Fibrosis, Thrombotic/Thromboembolic Complications, Lack or Loss of Response to Nplate®, Hematological Malignancies and Progression of Malignancy in Patients with a Pre-existing Hematological Malignancy or Myelodysplastic Syndrome (MDS).

■ Nplate® is not indicated for the treatment of thrombocytopenia due to MDS or any cause of thrombocytopenia other than chronic ITP.

■ Monitor CBC’s, including platelet counts and peripheral blood smears, prior to initiation, throughout, and following discontinuation of Nplate® therapy.

■ Nplate® is available only through a restricted distribution program called Nplate® NEXUS (Network of Experts Understanding and Supporting Nplate® and Patients) Program.

■ In the placebo-controlled studies, headache was the most commonly reported adverse drug reaction.

Please see Brief Summary of Prescribing Information on adjacent page.