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**SEVERE CHRONIC NEUTROPENIA INTERNATIONAL REGISTRY  
PROTOCOL****UW****Introduction**

The Severe Chronic Neutropenia International Registry (the Registry, SCNIR) is an organization dedicated to improving understanding and treatment for diseases causing severe chronic neutropenia, i.e. conditions with blood neutrophil levels less than  $0.5 \times 10^9/L$  for months or years. These diseases include various forms of congenital neutropenia, cyclic neutropenia, autoimmune neutropenia and idiopathic neutropenia. The Registry was initiated under sponsorship from Amgen, Thousand Oaks, CA, in 1994 to monitor the clinical course and long-term treatment of subjects with severe chronic neutropenia (SCN) after controlled clinical trials demonstrated the effectiveness of granulocyte colony-stimulating factor (G-CSF) for the treatment of these conditions. Subsequently, the National Institutes of Health became the principal sponsor of the Registry, with additional support from Amgen and private resources. The Severe Chronic Neutropenia International Registry (SCNIR) has two offices, one in Seattle and the other in Hannover, Germany. The offices work separately and under the auspices of their respective universities and IRBs. Only de-identified data/information is exchanged between the offices.

**Objectives**

The original objectives were to document the clinical course of severe chronic neutropenia and develop a database on the safety and efficacy of long-term treatment with G-CSF and other therapies. Additional goals were to establish a physician network to increase the understanding of SCN.

The Registry has successfully developed its database on efficacy and safety of treatment of SCN, and its resources have been extremely valuable for defining the genetic, molecular and cellular basis for cyclic and various causes of neutropenia. The current objectives of the Registry are:

1. Document the clinical course of SCN subjects and their responses to therapy.
2. Determine the incidence and outcome of various clinical events associated with SCN and its treatment including: a. osteoporosis; b. vasculitis; c. glomerulonephritis; d. splenomegaly/hepatomegaly; e. cytogenetic abnormalities; f. myelodysplastic syndrome; g. leukemia.
3. Evaluate the outcome for pregnancies in SCN subjects, including subjects receiving various therapies for their neutropenia.
4. Evaluate the effectiveness of hematopoietic transplantation as a treatment for SCN.
5. Serve as a comprehensive information resource for the education of physicians, subjects and families interested in SCN.

As of September 2012, there are approximately 1300 subjects enrolled in Seattle and 700 enrolled in Hannover.

Continued enrollment is important to increase the diversity of enrollees, particularly subjects with uncommon inherited conditions associated with SCN. In addition, continued enrollment is important for studies on etiology and pathogenesis of SCN and the evolution of some subjects to leukemia.

## **Subject Eligibility**

Inclusion Criteria – Subjects are eligible for enrollment if they meet the following criteria:

1. A confirmed diagnosis of severe chronic neutropenia based on documented absolute neutrophil counts of less than  $0.5 \times 10^9/L$  on at least three occasions in the three months prior to enrollment.
2. For subjects with presumed cyclic neutropenia, documentation of at least two neutrophil cycles is preferred. Documentation should include the nadirs with neutrophil counts of less than 200 followed by a clear increase in the counts generally to at least 500 to 1000 followed by a second nadir, usually expected to occur at about three weeks after the first nadir, i.e., cycling with a three week periodicity. Documentation with at least six weeks of counts and two expected nadirs is preferred. Cases not showing clear oscillations will be categorized as congenital (if neutropenia or neutropenic complications appear to have occurred from birth) or idiopathic (if all symptoms in evidence point to an acquired disorder occurring after the first year of life).
3. Bone marrow aspiration consistent with the diagnosis of congenital, cyclic or idiopathic neutropenia. In all of these conditions, it is expected that the marrow aspirate evaluation at the time of neutropenia will show a deficiency of mature neutrophils. An exception is myelokathexis, a condition with large accumulations of neutrophils with pycnotic nuclei in the marrow. Bone marrow aspirates may show some dyspoiesis of the neutrophil lineage, but abnormalities of erythropoiesis or platelet formation are, in general, inconsistent with the diagnosis of SCN.
4. Normal cytogenetic evaluation. The only exception being cases of well documented severe congenital neutropenia with preferably previously documented normal cytogenetic evaluation will now be enrolled in the Registry at the time of evolution to leukemia.
5. History of recurrent infections (i.e., severe mouth ulcers, gingivitis and sinusitis).
6. Age greater than three months.
7. Independent of hematological parameters, subjects with the following diagnoses may be included: Shwachman-Diamond syndrome (SDS), glycogen storage disease type 1b (GSD1b), Barth syndrome, and Cohen's syndrome.
8. Subjects with moderately severe chronic neutropenia (i.e., ANC less than  $1.0 \times 10^9/L$ ) and recurrent severe infections (i.e., deep tissue infections of subcutaneous areas, lungs, liver, etc.).
9. Immune neutropenia with positive anti-neutrophil antibodies meeting criteria in 1, 3, 5 and 6.
10. All SCN subjects originally enrolled in Amgen-sponsored SCN studies.

## Exclusion Criteria

1. Neutropenia known to be drug induced
2. Primary myelodysplasia
3. Primary leukemia
4. Aplastic anemia
5. Known HIV disease
6. Systemic autoimmune diseases such as rheumatoid arthritis or systemic lupus erythematosus
7. Chemotherapy-induced neutropenia (within the last 5 years)

## **Enrollment Procedures**

Enrollment will occur through subject or physician referrals to the Severe Chronic Neutropenia International Registry (SCNIR) or, in Europe, through members of the SCNIR Liaison Physician Group, all of whom are specialists in the diagnosis and treatment of severe chronic neutropenia.

For subject enrollment:

The subject contacts the Registry office at 1-800-726-4463. To enroll, the subject will discuss the consent form with the Registry personnel. The subject then completes a set of subject registration forms. After the phone consent is completed, the registration forms and consent are sent to the Registry. These completed forms will be reviewed and sent to an SCNIR Advisory Board Physician for review and possible approval to the Registry.

For physician enrollment:

At IRB-approved sites, the subject's physician contacts the Registry office, one of the physicians on the Registry Advisory Board or in Europe, the appropriate member of the Liaison Physician Group in their home country. To enroll a subject, the physician is required to complete a set of SCNIR registration forms. The signed institutional consent form is also sent along with the registration forms to the Registry. All forms must be completed and reviewed by an Advisory Board Physician before the subject is enrolled in the Registry.

The enrolling diagnosis is reviewed and confirmed by the SCNIR Advisory Board Physician.

A protocol exception requires the subject's complete medical case history. The SCNIR Advisory Board Physician will review for possible approval and enrollment into the SCNIR.

The registration form requires: the name, telephone/fax numbers and address of the referring subject's physician, the signed consent (or documentation of signed consent), the name, demographic information, diagnoses for the subject, information on the significant clinical history of infections and other medical problems (i.e., splenomegaly, hepatomegaly), information on growth and development, information on the treatment history for the subject, including growth factor cytokine treatment, information on bone marrow and cytogenetic evaluations and bone density assessment, and records of the subject's blood counts and other hematological tests. A

clinical summary of the subject's problems with neutropenia may also be included. In addition, information is requested regarding neutropenia, leukemia, other blood disorders for all family members, whether the individuals listed are living or deceased.

Enrollment forms are reviewed by an SCNIR Advisory Board Physician. If further information is needed the information will be requested. After enrollment, annual follow-up forms requesting information regarding the health status are sent to the enrolling subject or physician. Subjects are encouraged to communicate to the Registry and their physician about serious health events occurring between annual follow-ups.

### **Bone Marrow Slides**

With each new registration, the Registry requests at least one bone marrow slide preferentially from the diagnostic bone marrow aspirate or any other bone marrow sample prior to the onset of any G-CSF therapy. These slides are requested to assist with the diagnosis of SCN, if necessary. If the referring physician requests the slides back, they will be returned.

### **Privacy and Confidentiality**

Subjects' names will be kept on a password-protected database and will be linked to the research data with a study identification number used for this research only. All data will be entered into a password-protected computer kept in a locked room at the Registry. Data will be stored in locked file cabinets which are located in an office space that is locked at all times and will be maintained for a minimum of thirty years after the completion of the study. Only the researchers will have routine access to this information. Researchers not attached to the Registry study will not have access to this information.