



BACKGROUND

African Americans Banned from Early Hepatitis C Clinical Trial

What is the clinical trial called?

The formal title is *Study P03659: PEG-Intron/REBETOL vs. PEG-Intron/SCH 503034 With and Without Ribavirin in Chronic Hepatitis C HCV-1 Peginterferon alfa/Ribavirin Nonresponders: A SCH 503034 Dose-Finding Phase 2 Study*. It is sponsored by Schering-Plough Corporation.

What is the study about?

Phase 2 studies test different doses of a new drug in a small number of volunteers to determine the safest effective dose for further study. Study P03659 includes 365 participants with chronic hepatitis C virus (HCV). Seven different doses of the new drug are being studied. The study was originally designed to test six doses of the new drug in 300 participants, but a recently announced amendment to the study adds a higher-dose to be tested in 65 participants, 15 of whom will be African American.

The study is looking at harder-to-treat HCV patients. In this study, harder-to-treat patients are nonresponders (people who did not have a successful response to previous HCV treatment as measured by little or no decrease in the amount of virus in their blood) *and* who have genotype 1 (the most common genetic variant of HCV in the US and one that is less responsive to current treatment).

What drugs are being used in this study?

- **SCH 503034** is a new investigational drug for the treatment of HCV that is being developed by Schering-Plough. The drug is a member of a new class of drugs to treat HCV called protease inhibitors. Similar to the protease inhibitors used to treat HIV, SCH 503034 is designed to inhibit the protease enzyme of the hepatitis C virus to interfere with viral replication. It is likely that HCV protease inhibitors will need to be used in combination with other drugs rather than alone.
- **PEG-Intron (pegylated interferon alfa-2b)** is used to treat HCV. It is administered by injection, usually once a week, to boost the body's immune response against HCV.
- **Rebetol (ribavirin)** is an oral antiviral that is taken twice a day. It is used in combination with an interferon such as pegylated interferon alfa-2b to increase the effect of the interferon.

What is the problem with Study P03659?

Schering-Plough excluded African Americans from participating in the early phase of this study. The protocol was recently amended to add a token 15 African Americans, all assigned to the highest dose arm being studied rather than being randomized to the various arms as all of the other participants are. The high-dose arm will include 65 participants rather than the 50 in the other arms. This highest dose arm may turn out to be the most effective one, but it may also have the most side effects. The inclusion of fifteen participants is too small to draw any meaningful conclusions about the effects of the drug in African Americans.

Schering-Plough can use the data (if it is favorable) or ignore it (if it is not favorable) to spin the study results when comparing the effects of the higher dose in African Americans to those of the other participants. African Americans should not be treated any differently than any other population in this or any other study unless there is a compelling safety concern. With adequate informed consent, all trial participants should have been randomly assigned to the different doses of the study. In such a design, the results would give Schering-Plough and the community and idea of the safety and effectiveness of the experimental drug at various doses in all trials participants, whatever their race. As designed, the study is unethical and does not represent the populations that will use the drug if it is eventually approved by the Food and Drug Administration.

What reason does Schering-Plough give for treating African Americans differently in the study?

Company representatives stated that they wanted “genetic homogeneity” in the trial population. The study excludes African Americans, yet allows non-Americans of African ancestry. This does not make sense.

Schering-Plough representatives also stated verbally (but not in any written materials, including the study protocol) that the company excluded African Americans from the study because African Americans often have lower baseline neutrophil counts than those of people of other races. Neutrophils are a type of white blood cell that forms a primary defense against bacterial infections. With a low neutrophils count, the body cannot defend itself adequately against bacterial infection. Pegylated interferon (one of the drugs used in the study) decreases neutrophil counts in many patients on treatment. There is controversy concerning the importance of the decrease.

Per the written study summary, having baseline neutrophils $\geq 1,500/\text{mm}^3$ is an inclusion criterion for *all* study participants. This reasonable inclusion criterion belies the company’s position that African Americans were excluded from the study due to safety concerns. Having a healthy neutrophil count was already listed as an inclusion criterion, so there was clearly no safety rationale for the exclusion of all African Americans from the study for fear that some might have low neutrophil counts. Schering-Plough has not cited any other safety concerns to justify the racial exclusion.

In a March 17 teleconference with community members, a Schering representative said that this was the most “efficient” way to conduct the study. Unfortunately, this seems to be a truthful, although irresponsible, description of the company’s strategy. It is always faster and more efficient *not* to study the effects of a drug in a population than to include that population in a study. In this context, “efficiency” seems to mean that the company did not want to include enough African Americans in Study P03659 to provide the power necessary to gain meaningful results. The company also wanted to avoid including only a few African Americans in each dosing arm for fear that the individual responses might lower the overall effectiveness of the drug in the separate arms.

Doesn't the exclusion criterion protect African Americans, who often have more side effects from interferon treatment compared to other races do?

We cannot know whether African Americans benefit from SCH 503034 unless they are given the same opportunity to participate in the full range of the study as other participants. *Not* studying how African Americans respond to the different doses is more likely to endanger rather than help this population. African Americans are excluded from receiving the lower doses of the

drug and are only being given the highest dose, which is likely to have more common and severe side effects.

Isn't the racial exclusion okay since Schering-Plough says that it will include African Americans in the Phase 3 clinical trials of SCH 503034?

Phase 3 trials study how well a drug works in a large number of people. However, Phase 3 trials are conducted after Phase 2 studies are completed, once several doses of the drug have been studied to identify the one that is both safest and most effective. Safety comes first. If Schering-Plough expects SCH 503034 to be as safe in African Americans as in other populations in order to include them in Phase 3 trials (as required by law), why limit their participation in the Phase 2 trial?

What studies show that current HCV treatment is less effective overall in African Americans than in other racial groups and describe side effects by population?

The most useful studies include:

- Muir AJ, Bornstein JD, Killenberg PG; Atlantic Coast Hepatitis Treatment Group. *Peginterferon Alfa-2b and Ribavirin for the Treatment of Chronic Hepatitis C in Blacks and Non-Hispanic Whites*. N Engl J Med. 2004 May 27;350(22):2265-71.
- Jeffers LJ, Cassidy W, Howell CD, Hu S, Reddy KR. *Peginterferon Alfa-2a (40 kd) and Ribavirin for Black American Patients With Chronic HCV Genotype 1*. Hepatology. 2004 Jun;39(6):1702-8.