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No. 30 – Development of New Drugs for

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Title: **Development of New Drugs for ITP**

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Much has been written in previous issues of The Platelet about new drugs that can increase platelet counts in patients with ITP by stimulating bone marrow production of platelets. Romiplostim (formerly known by its investigational name, AMG 531) will be the first of this new class of drugs to be available for ITP patients in the US in June 2008. Eltrombopag will be approved for use soon thereafter. The the extensive investigations that lead to approval of these drugs documents the extraordinary measures taken to assure that they are both effective and safe. We can tell the story of the development of romiplostim, because we have been involved with these studies from the beginning. The steps in the development of eltrombopag have been similar.

The initial study of romiplostim began many years before approval. First, romiplostim was shown to be effective and safe in multiple species of animals. Next it was shown to be effective and safe in normal human volunteer subjects. The studies in patients with ITP then began 7 years ago and involved three stages of development. First, a few patients were given gradually increasing doses of romiplostim to determine the minimum dose that would usually increase the platelet count. In the second phase of these studies, a few patients were given a series of 6 weekly treatments, at the appropriate doses determined by the initial study. In this second phase of experiments, some patients received a placebo treatment, an injection of saline that would be expected to have no beneficial or harmful effect, rather than romiplostim. Treatment of patients with a placebo is an essential part of these investigations, because many people have common symptoms of headache, tiredness, or just not feeling well. Comparison of groups of patients who received the experimental drug to patients receiving on the placebo helps to identify adverse effects that are caused by the experimental drug. The incentive for patients to participate in these studies, even if they were chosen to receive a placebo, was that they were then eligible to participate in a long-term continuing treatment study with romiplostim. Since it was soon apparent that romiplostim increased platelet counts in most patients with ITP, its effectiveness was confirmed as was long-term safety over several years. Finally, the third phase of the clinical trials was a larger study of still more patients with ITP treated for six months, either with romiplostim or a placebo. Two such studies were done, one in patients who had failed splenectomy and the other in patients who had not yet had splenectomy. The results of both of these studies demonstrated conclusively that romiplostim can effectively increase platelet counts to safe levels in most patients with ITP, even when splenectomy and multiple other treatments were unsuccessful. These were the studies that provided the data supporting approval by the US Food and Drug Administration (FDA).

Documentation of safety is always more difficult than documentation of effectiveness. This is because a good effect of a new drug should occur in most patients, while complications caused by a new drug may be rare but still very serious. Even though romiplostim has been given to approximately 400 patients with ITP, some of them for over 3 years, these represent small numbers and short durations compared to the expected wide use of romiplostim following FDA approval. Therefore the FDA has established a requirement for very careful surveillance of all patients who receive romiplostim. First, doctors will receive romiplostim only for patients whom they certify as having ITP. This is because romiplostim may have different and more serious side effects in patients with thrombocytopenia caused by other diseases. Second, patients must agree to regular follow-up, in order to document any significant or unexpected toxicity that may be caused by romiplostim. This restricted distribution is necessary to assure the safety of this new agent.

Like many new drugs, romiplostim is approved only for use in adults, because the patient studies during its development were performed only in adults. This is always the case in order to provide protection for children. But this also means that romiplostim will at least initially be unavailable for children.

This experience describes the enormous effort required to develop a new treatment. Such effort is extremely costly so it is not a surprise that new drugs are so expensive. Although there is a sense of urgency to make new effective and safe treatments available for patients in need, regulatory agencies such as the FDA have a critical responsibility to protect patients from drugs that may have harmful side effects. The story of the development of these new drugs for ITP contrasts with the use of non-approved agents, such as alternative and complementary medicines, which do not undergo rigorous testing before their use in patients. Although the process can be slow, the result is confidence in the effectiveness and safety of new drugs that should benefit many patients with ITP.