

# The Clinical Corner

## Update on Oral Blood Thinners in Development

Stephan Moll, MD, University of North Carolina, Chapel Hill, NC  
Jeffrey I Weitz, McMaster University and Henderson Research Center, Hamilton, ON, Canada

At present, warfarin (coumadin®) is the only oral blood thinner (anticoagulant) available in the U.S. that is approved by the Federal Drug Agency (FDA). As many patients know, warfarin therapy can be quite inconvenient, since (a) regular monitoring of its blood thinning effect is needed (via the protime or INR—International Normalized Ratio), (b) it can be difficult to find the right warfarin dose for an individual patient, (c) INRs may fluctuate, (d) vitamin K in the diet can influence the INR, and (e) many other drugs interact with warfarin and increase or decrease the INR.

Several new oral blood thinners that do not require monitoring of their blood thinning effect are in development. If they come onto the market, they will make life much easier for patients who require long-term blood thinning medication. Exanta® (Ximelagatran; by Astra-Zeneca) was the drug furthest along in clinical development. However, in October 2004 the FDA decided not to approve Exanta® (see NATT spring 2005 newsletter). Although Exanta® was approved for short-term use in Europe, the drug was withdrawn from the world market in February 2006 because of potential liver problems that could be fatal. Astra-Zeneca is now focusing on the development of a newer blood thinner, that is presently being tested in clinical trials (table).

The race continues among several pharmaceutical companies to be the first to get a new oral blood thinner clinically tested, approved, and onto the market. Several drugs are presently being studied in human trials. It is too early to speculate or conclude, how good these drugs are, which ones might eventually lead to FDA approval, and which one might be the first on the market. The new blood thinners are divided into two classes, depending on their blood thinning mechanism. One class of drugs blocks the clotting protein thrombin (also called “factor IIa”) and the drugs are, therefore, called anti-thrombins or anti-IIa drugs. The other class of drugs blocks the clotting protein factor Xa and the drugs are, therefore, called Xa-inhibitors or anti-Xa drugs. There is no scientific reason why one class should be safer or more effective than the other. Clinical trials will determine whether there is a difference between them and which one is the best (most effective and safest).

Drugs in development have to go through rigorous and extensive clinical trials before they can receive FDA approval and come onto the market. Clinical trials are divided into 4 phases:

Phase 1: safety trial, often in healthy volunteers.

Phase 2: dose-finding trial, in which

several different investigational drug doses (typically around 4 doses) are compared with a well established drug. In the case of oral blood thinners, the control is warfarin.

Phase 3: large trial usually involving thousands of patients; the investigational drug is compared with established treatment. In phase 3 trials, only one dose of study drug is tested—the one that has been determined to be optimal in the phase 2 trials. The results of the phase 3 trials, if favorable, lead to FDA application for approval of the drug.

Phase 4: These trials are done after the drug has been FDA approved. The purpose is to collect additional information on a drug’s risks, benefits, and optimal use.

All the new oral blood thinners other than Exanta® are in earlier stages of clinical development. Thus, these drugs are at least 2 to 5 years away from potentially coming onto the market. The table lists condensed information about developmental oral blood thinners that have entered human trials. It is difficult to obtain information about new drugs because of confidentiality issues. Furthermore, some companies do not immediately publish their clinical study results. This table may, therefore, be incomplete.

After the disappointment in 2004 of not seeing Exanta® FDA approved, 2006 is exciting: several of the new oral blood thinners have gone into large phase 3 clinical trials. Warfarin, with its cumbersome blood monitoring requirements and food and drug interactions, may, at some point, be replaced by better and more user-friendly drugs.

### New oral blood thinners in development, that are presently being studied in humans

	Drug name	Company	Clinical trial phase	Mechanism
1	<b>Dabigatran</b>	Boehringer-Ingelheim	Phase 3	anti-IIa
2	<b>AZD 0837</b>	Astra-Zeneca	Phase 2	anti-IIa
3	<b>Bay 59-7939 = Rivaroxaban</b>	Bayer	Phase 3	anti-Xa
4	<b>LY517717</b>	Eli-Lilly & Company	Phase 2	anti-Xa
5	<b>YM150</b>	Astellas Pharma Europe B.V.	Phase 2	anti-Xa
6	<b>Odiparcil</b>	Glaxo-Smith-Kline	Phase 2	indirect anti-IIa
7	<b>DU-176b</b>	Daiichi	Phase 2	anti-Xa
8	<b>Apixaban (BMS-562247)</b>	Bristol-Myers-Squibb	Phase 2	anti-Xa
9	<b>TGN-167</b>	Trigen	Phase 1	anti-IIa
10	<b>Exanta® (Ximelagatran)</b> (development stopped)	Astra-Zeneca	Phase 3	anti-IIa
11	<b>Razaxaban</b> (development stopped)	Bristol-Myers-Squibb	Phase 2	anti-Xa