Overview
Portola Pharmaceuticals is focused on the development and commercialization of novel therapeutics to meet patient needs in thrombosis, other hematologic disorders and inflammation. Our current development-stage portfolio includes wholly-owned and partnered products.

Thrombosis
Prophylaxis against all forms of thrombosis is a major medical need throughout the developed world. For example, in the G7 countries—the United States, Japan, France, Germany, Italy, Spain and the United Kingdom—existing medical guidelines recommend that a population of approximately 46.4 million patients receive some form of anticoagulation drug therapy to reduce their risk of thrombosis. The largest category of patients at risk for thrombosis is the acute medically ill, whose risk is increased for those patients immobilized for more than a few days or with other risk factors. Our two lead programs address significant unmet medical needs in the area of thrombosis:

• **Betrixaban**: A novel, oral, once-daily inhibitor of Factor Xa currently being evaluated in the global, pivotal Phase 3 APEX Study for extended duration venous thromboembolism (VTE) prophylaxis in acute medically ill patients. Currently, there is no anticoagulant approved for extended duration VTE prophylaxis in this population.

• **PRT4445**: A recombinant Factor Xa inhibitor antidote designed to reverse the anticoagulant activity in patients treated with a Factor Xa inhibitor who suffer an uncontrolled bleeding episode or undergo emergency surgery. PRT4445 has completed the first in a series of Phase 2 proof-of-concept studies.

Betrixaban
- Oral small molecule anticoagulant that directly inhibits the activity of Factor Xa, an important validated target in the blood coagulation pathway
- Portola has worldwide rights to develop and commercialize betrixaban.

Key Characteristics
- Specifically designed for chronic, once-a-day treatment, with a half-life that supports true, once-daily dosing and a low peak-to-trough drug concentration ratio that minimizes anticoagulant variability
- Primarily eliminated unchanged in the bile; studied in patients with all degrees of renal function, including those with severe renal impairment (excluding dialysis patients)
- Minimally metabolized through the Cytochrome P450 enzyme system, which may result in low potential for CYP-related drug interactions
- Reversible with PRT4445, Portola’s recombinant Factor Xa inhibitor antidote

Potential Indications
Extended duration VTE prophylaxis in acute medically ill
Betrixaban (continued)

**Status**

*Phase 3*

The APEX Study (Acute Medically III VTE Prevention with Extended Duration Betrixaban) is currently evaluating betrixaban for hospital and post-discharge prevention of venous thromboembolism (VTE) in high-risk acute medically ill patients. The study is enrolling approximately 6,850 patients at more than 400 study sites throughout the world.

**Phase 1 and 2**

Betrixaban has been evaluated in 22 Phase 1 and Phase 2 clinical studies involving 1,411 human subjects, 1,200 of whom received betrixaban, including more than 100 subjects for six months or more. In three Phase 2 studies, betrixaban was evaluated in specific patient populations relative to commonly used anticoagulants. Consistent with the development of other antithrombotic agents, these studies were not designed to demonstrate a statistically significant difference between groups for the studied outcomes. The betrixaban Phase 2 studies were instead designed to demonstrate evidence of an anticoagulant effect and relative safety compared to an established comparator. In these clinical studies:

- Betrixaban was well tolerated in diverse patient populations with comparable or better tolerability as compared to warfarin and enoxaparin.
- Betrixaban achieved clinically relevant anticoagulant activity with comparable or less bleeding risk than existing agents.
- Betrixaban demonstrated predictable pharmacokinetic and pharmacodynamic activity.

**PRT4445**

- Recombinant Factor Xa inhibitor antidote
- Portola has worldwide rights to develop and commercialize PRT4445.

**Key Characteristics**

- Acts as a Factor Xa decoy that binds to Factor Xa inhibitors in the blood. Once bound to PRT4445, the inhibitors are unable to bind to and inhibit native Factor Xa. The native Factor Xa then becomes available to participate in the coagulation process and restore hemostasis, or normal clotting.
- Preclinical and Phase 1 studies suggest that PRT4445 has the potential to be a universal reversal agent for all Factor Xa inhibitors.

**Potential Indications**

Reverse Factor Xa inhibitor anticoagulant activity in patients treated with a Factor Xa inhibitor who suffer an uncontrolled bleeding episode or undergo emergency surgery

**Status**

- The first in a series of Phase 2 proof-of-concept studies was initiated in December 2012 to evaluate the safety and activity of PRT4445 in healthy volunteers who have been administered one of several Factor Xa inhibitors, including apixaban, rivaroxaban and betrixaban.
- Portola announced efficacy and safety data from the first study in the series in May 2013. Analysis of anticoagulation markers and plasma concentration levels of apixaban in blood samples taken from the subjects indicates that PRT4445 produces a rapid, sustained and dose-related reversal of the anticoagulant activity of apixaban. In addition, no adverse events were reported.
- Portola is conducting a separate Phase 2 study with PRT4445 and the Factor Xa inhibitor rivaroxaban and expects to complete it in 2013.

Hematologic Disorders/Inflammation

Our early-stage development programs are focused on developing small molecule kinase inhibitors for the treatment of hematologic cancers and inflammatory diseases. Kinases are enzymes that act on and modify the activity of different proteins. Syk and JAK are clinically validated kinase targets involved in key signaling pathways that are important in certain hematologic cancers and inflammatory disorders. We have focused on the discovery and development of specific inhibitors of Syk and dual inhibitors of both Syk and JAK based on the unique roles of these kinases in non-Hodgkin’s lymphoma (NHL), chronic lymphocytic leukemia (CLL), allergic asthma, rheumatoid arthritis and other inflammatory diseases. Our programs include:

- **PRT2070**: An orally available, potent inhibitor of Syk and JAK
- **PRT2607** and other Syk-selective inhibitors

**PRT2070**

- Novel, oral dual Syk-JAK kinase inhibitor
- Portola has worldwide rights* to develop and commercialize PRT2070.

**Key Characteristics**

- Highly potent inhibitor of both Syk and JAK

**Potential Indications**

Certain B-cell hematologic cancers, with a particular focus on patients who have mutations that cause failure or relapse with existing treatments, as well as treatments currently in development

**Status**

- Preclinical testing showed inhibition of Syk and JAK, via PRT2070, was active in a broad panel of B-cell lymphoma cell lines. PRT2070 was more effective than Syk-specific inhibition in these cell lines, suggesting that PRT2070 may be useful in the treatment of a broad range of B-cell lymphomas, including patients with diffuse large B-cell lymphoma (DLBCL), an aggressive form of non-Hodgkin’s lymphoma (NHL), and patients with hard-to-treat mutations.
- Portola plans to file an investigational new drug application (IND) with the FDA in order to advance PRT2070 into a Phase 1/2 clinical study in patients with relapsed or refractory chronic lymphocytic leukemia (CLL) and non-Hodgkin lymphoma (NHL), including patients with diffuse large B-cell lymphoma (DLBCL).

*Hematologic cancer and other systemic indications are wholly owned by Portola. Certain nonsystemic indications rights are shared 50/50 with Acxiem.

**PRT2607 and Other Syk-Selective Inhibitors**

- Novel, oral small molecules that selectively inhibit Syk
- Partnered with Biogen Idec.

**Key Characteristics**

- Highly specific oral inhibitors of Syk, an important mediator of immune response in a number of different types of immune cells. Syk plays a critical role in mast-cell signaling and activation, which are central to immune system over-activation and resultant airway constrictions in asthma.

**Potential Indications**

Allergic asthma, inflammatory diseases

**Status**

- Biogen Idec is leading the pre-clinical study of PRT2607 and other highly selective Syk inhibitors for allergic asthma and other inflammatory disorders.