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INITIATION REPORT

Pharmaceutical Industry ● November 22, 2011

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LIGAND PHARMACEUTICALS (NASDAQGM: LGND)

- **Ligand's investments are about to pay off handsomely:**
  - **Promacta sales are rising rapidly around the world and new indications are under development.** The thrombocytopenia drug is gaining market share for ITP as the drug has entered new territories around the world and a new indication is likely – hepatitis C.
  - **The Captisol platform opens new opportunities to partner with other drug companies at no risk.** The modified cyclodextrin has passed regulatory muster and numerous compounds now in clinical trials use it to ensure proper bioavailability.
  - **One drug may get an early approval.** Onyx has submitted an NDA for carfilzomib for multiple myeloma based on Phase 2 data that has looked impressive.
- **Operations are turning profitable** on larger revenue streams and tight cost controls.
- **More partnering agreements are likely,** given Ligand's R&D pipeline and novel excipient.

We are initiating coverage of LGND shares with a BUY rating and a 12-month price target of $18.

Share Price (11/18/2011)	$10.59
52-Week Price Low / High	$8.14 - $16.24
Mkt. Capitalization (issued)	$208.3 million
Shares Outstanding (issued)	19.67 million
12-month Target Price	$18.00
Average Daily Volume (3 mos.)	204,366
Website	www.ligand.com
Est'd 2011 Earn's (Loss)/shr	($0.45)
Est'd 2012 Earn's (Loss)/shr	$0.05

Source: Nasdaq.com

Ligand Pharmaceuticals (NasdaqGM: LGND) is a pharmaceutical company that focuses on the discovery, reformulation, and partnering of therapeutic agents. The product portfolio includes more than 60 compounds in development (>50 partnered) and on the market (9). Internally developed drugs include Glaxo-SmithKline's Promacta®, Pfizer's Conbriza®, and Merck's dinaciclib.

The Company's proprietary excipient, called Captisol®, facilitates the solubilization of compounds that otherwise may not be suitable drug candidates. Indeed, formulations based on this inert material, which is a modified cyclodextrin, are able to improve both the efficacy and side-effect profile of a compound. Among the drugs that use Captisol are Baxter International's Nexterone® and Onyx Pharmaceutical's carfilzomib.

Ligand shares constitute a means of investing in a diversified, revenue-generating drug portfolio. We expect multiple valuation-driving events in 2012 and are initiating coverage with a BUY recommendation and target share price of $18.

INVESTMENT THESIS

Revenues from Ligand's product portfolio are on the rise. Ligand is gaining revenue via licensing agreements already in place for more than 50 drugs, including some based on its proprietary excipient Captisol. The September quarter included sales of Nexterone, a Captisol-enabled drug, for the first time; GlaxoSmithKline is making headway with Promacta – annual sales should surpass $100 million this quarter; and the China-based Chiva Pharmaceuticals recently licensed the osteoporosis drug Fablyn for a European launch next year. The wild card for 2012/2013 is Onyx's carfilzomib, which may be approved for multiple myeloma on Phase 2 data. If not, 2013 should mark this impressive drug's debut.

Operations are about to turn profitable. One of Ligand's goals for 2011 has been to turn cash-flow positive and profitable by year end. We believe that goal will be met in the December quarter. The growing revenues from Captisol sales and royalties are clearly a plus. Milestones from new clients, such as Chiva, and existing licensees that include many of the largest pharmaceutical companies are another. In addition, expenses are under tight control at Ligand, as management has taken steps to cut costs and invest in R&D with a close eye on the balance between the risk and the potential reward of each project.

Investors can expect important news on product development in the months ahead. With more than 60 programs in all phases of development through commercialization, the Company has ample topics of discussion. But more specifically, there will be important news on the latest Promacta clinical trial, Onyx's carfilzomib, Chiva's launch of Fablyn, clinical progress on novel compounds, such as Merck's dinaciclib, and probably more licensing agreements. Then, too, Ligand has a track record of sound acquisitions, so another deal would not be a surprise.

Portfolio managers should appreciate Ligand executives' approach to drug development. The Company has created a portfolio of more than 60 programs that span all stages of development from preclinical through FDA approved. Risk is mitigated in several ways: (i) by the size of the portfolio, (ii) by the diversity of indications being targeted, and (iii) by investing only enough in any program to entice a partner to agree to complete development in exchange for licensing-related fees (i.e., upfront fee, milestone payments, royalties, and sales of Captisol when appropriate). This has enabled Ligand to minimize its capital requirements over the past four years while it was making progress in the lab and clinic. With more products coming to market and sales of existing drugs increasing, the Company should have greater strategic flexibility, though we do not expect a change in its business model.

This stock should hit a new high within the next 12 months. Ligand shares sold off on November 8th, the day after two clinicians involved in Phase 3 trials of Promacta decided to provide top-line news from the ENABLE 2 study at the annual meeting of the American Association for the Study of Liver Disease. The preliminary safety data from that hepatitis C trial spooked the investment community. We believe the sell-off was a mistake. First, the "safety signal" hadn't been analyzed in any detail, meaning that some events probably were not related to the drug but were in the top-line data. Second, the enrolled patients were suffering from advanced liver disease, a condition that is known to cause serious medical problems, including a blood flow anomaly in the portal vein of the liver that can cause asymptomatic blood clots that are nonetheless visible with Doppler ultrasound and are reportable safety events. Third, all patients were treated with Promacta prior to commencement of antiviral or placebo therapy and during that pretreatment period, there was no evidence of thrombosis. This is consistent with prior trials. Finally, the placebo group in the ENABLE 2 study did not experience thromboembolic events at the normal, expected rate. If they had, the investigators at the meeting pointed out that the trial would have no "safety signal." Hence, the recent decline in Ligand's share price presents a buying opportunity.

Importantly, the Company is making solid progress with more products generating larger revenues, while it maintains a tight grip on its own operating expenses. This combination should turn operations profitable soon and provide a growing source of income in the years ahead. Hence, we are initiating coverage of Ligand Pharmaceuticals (NasdaqGM: LGND) with a BUY recommendation and a 12-month price target of $18 per share.

TABLE OF CONTENTS

MANAGEMENT TEAM

John L. Higgins, President, Chief Executive Officer, & Director

- Joined Ligand Pharmaceuticals in 2007 and now has over 18 years of experience in the pharmaceutical industry. Prior to Ligand, he served in executive positions with Connetics Corporation and BioCryst Pharmaceuticals.
- Serves as Chairman of CoMentis, Inc. and is a member of the audit committee and board of directors of Techne Corporation and BioCryst Pharmaceuticals. Has served previously on the boards of numerous public and private corporations.
- Gained experience in financial transactions while serving as a member of the healthcare investment banking team of Dillon Reed & Company.

Matthew W. Foehr, Executive Vice President & Chief Operating Officer

- Has over 17 years of experience, having held various executive positions with GlaxoSmithKline, Stiefel Laboratories, Connetics Corporation, which include managing global R&D operations.
- Joined Ligand Pharmaceuticals in April 2011.

Charles Berkman, JD, Vice President, General Counsel and Secretary

- Has over 18 years of experience, having held various legal positions with Ligand, Baker and McKenzie and Lyon and Lyon
- Joined Ligand Pharmaceuticals in 2001 and has served in his current capacity since 2007.

Syed Kazmi, PhD, MBA, Vice President, Business Development and Strategic Planning

- Joined Ligand Pharmaceuticals in 1995 and has served in his current capacity since July 2007.
- Has over 23 years of experience in the pharmaceutical industry that includes drug development in the fields of endocrinology and inflammation with Johnson & Johnson.

John Sharp, CPA, Vice President, Finance and Chief Financial Officer

- Assumed his current position in 2007, with 15 years of experience in accounting.
- Served in executive positions in finance/accounting with Sequenom and Diversa Corporation, after six years with the public accounting firm PriceWaterhouseCoopers.

BOARD OF DIRECTORS

John Kozarich, Ph.D., Chairman of the Board

- Has served on Ligand's board since 2003 and has held executive positions with Merck Research Laboratories and faculty positions at the University of Maryland and Yale University
- Currently serves as the Chairman, President, and a director of ActivX Biosciences, a subsidiary of Tokyo based Kyorin Pharmaceutical Company and biotechnology professor at the Scripps Research Institute.

Jason M. Aryeh, Director

- Has served on Ligand's board since 2006.
- Is the founder & managing partner of Jalaa Equities, a biotech hedge fund, and serves on the boards of Nabi Biopharmaceuticals, Myrexis Inc., CorMatrix Cardiovascular, and the Cystic Fibrosis Foundation's Therapeutics Board.

Todd C. Davis, Director

- Has been on the Ligand board since 2007 and serves as a managing director for Cowen Healthcare Royalty Management after a career in the pharmaceutical industry with Abbott Labs and Elan.

John L. Higgins, President, Chief Executive Officer, & Director

David M. Knott, Director

- Has more than 24 years of experience in the financial industry, where he currently serves as the Chief Investment Manager of two related hedge funds, Knott Partners Management and Dorsett Management. Also serves on the board of directors of Paramount Resources

John L. LaMattina, Director

- Joined the Ligand board in 2011 after a 30-year career with increasing managerial responsibility in drug development at Pfizer.

Sunil Patel, Director

- Serves as the Vice President of Corporate Development at OncoMed Pharmaceuticals, having 17 years of experience in the pharmaceutical industry with BiPar Sciences, Allos Therapeutics, Connetics, Abgenix and Gilead Sciences.

Stephen L. Sabba, M.D., Director

- Has served on the Ligand board since 2008 and is presently a research analyst and Bio Fund Manager with Knott Partners Management.

A History of Savvy Acquisitions

In 2006 and early 2007, Ligand sold its pharmaceutical operations so that it would be able to focus on its strength, the discovery of new therapeutic candidates. By late February 2007, the Company had $415 million in cash on its balance sheet. A few weeks later, on March 21st, the board of directors declared a special dividend that returned $253 million in cash to Ligand stockholders and initiated a $100 million share repurchase program.

Since John Higgins assumed the positions of President and CEO in January 2007, Ligand has made four acquisitions that expanded its drug portfolio, gained drug screening technologies, brought in an excipient platform for future applications, and greatly increased the number of licensing agreements with the pharmaceutical industry. These assets have yielded significant revenues over the past four years, but more important, these acquisitions are about to help transform Ligand into a profitable drug company.

Dec,'08	Pharmacopeia for $55 million of cash, stock and contingent payments
Dec,'09	Neurogen for 4.2 million shares, thereby gaining the rights to a pipeline of drugs for CNS disorders and other indications
Jan,'10	Metabasis for $1.6 million, contingency payments based on outlicensing of Metabasis drugs (e.g., for viral infections, metabolic disorders, and vascular diseases), and an investment of at least $8 million in the Metabasis portfolio
May,'10	A 50% interest for $1.375 million in an IL-9 antibody program that underpins an asthma drug development program at **AstraZeneca**'s subsidiary MedImmune
Jan,'11	CyDex in $35.5 million deal that doubled the size of the product portfolio, secured rights to the Captisol platform, and gained a business that generated $16.3 million in revenue in 2010 and EBITDA of $7.6 million

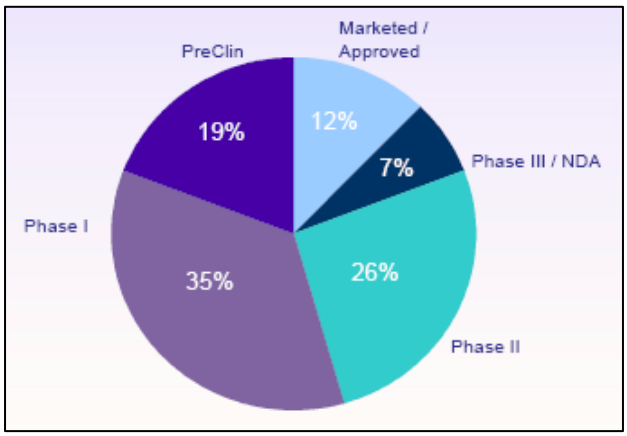
Near-Term Milestones

Q4,'11	Potential acceptance of Onyx Pharmaceuticals' carfilzomib NDA for review by the FDA
Q4,'11	Promacta worldwide sales surpass $100 million for the first time
Q4,'11	Ligand's operations turn cash flow positive and profitable
H1,'12	Presentation of ENABLE 1 & 2 data at the 47th Annual Meeting of the European Association for the Study of the Liver
Mid-'12	**The Medicines Company** initiates pivotal 505(b)(2) trial of Captisol-formulated clopidrogel (an i.v. preparation of **Bristol-Myers Squibb's** Plavix®)
H2,'12	Chiva launches Fablyn in Europe
2012	Merck initiates a Phase 3 clinical trial of dinaciclib
2012	GlaxoSmithKline submits a sNDA to gain regulatory approval of Promacta for hepatitis C and advanced liver disease
2012	Ligand secures a partner to develop Captisol-formulated melphalan or initiates pivotal 505(b)(2) clinical study

LIGAND'S BUSINESS MODEL

The Company has a unique strategy, one that has enabled it to build its business over the past few years while the industry went through a consolidation that saw even large corporations acquired and many small companies fail. The key to Ligand's success has been its strict discipline in minimizing its investment in any one project. This has led the Company to invest where a small amount of capital would achieve a valuation inflection point and/or render a program more attractive to a partner. In accordance with this strategy, management has outlicensed more than 50 programs for development by partners and has continued another 10 or so with its own funds. A breakdown of the portfolio by stage of development is presented in Figure 1.

Figure 1. Ligand's Product Portfolio by Phase of Development



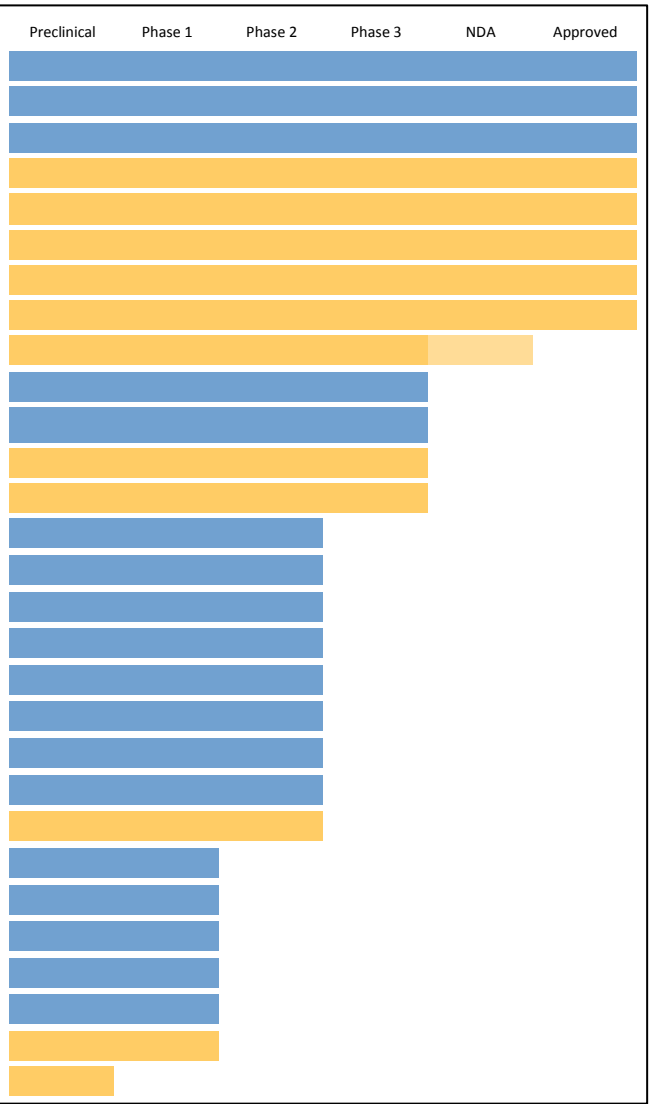
Source: Ligand Pharmaceuticals

This portfolio includes compounds that were discovered by Ligand or the companies that it has acquired over the years and others that have been formulated with an excipient created by its most recent acquisition, CyDex. (See Table 1.) Many in the latter group would never have been developed if not for the enhanced solubility achieved with CyDex's Captisol. The economics of deals involving these two groups of drugs are different for Ligand. Licensing agreements involving novel, internally developed compounds may include upfront fees, milestones and royalties based on the partner's sales. Captisol deals may include any or all of these, but they also include sales of Captisol to the partner. This distinction is important because sales of the excipient constitute a meaningful source of revenue as a drug is undergoing clinical trials, as well as after its commercial launch. Indeed, we estimate that Captisol sales will account for approximately 50% of Ligand's revenues in 2011.

In keeping with its strategy of minimizing its own investments, Ligand has engaged an experienced pharmaceutical manufacturer, Lisbon-based Hovione FarmaCiencia, to supply Captisol under a contract extends through 2019. Hovione has been producing the excipient at a manufacturing plant in Portugal thus far, but preparations are under way to supply it from a second site in Ireland soon. The agreement between the two companies is on a cost-plus basis that provides Ligand with a healthy gross margin in the range of 60%-65% on its sales to partners.

Table 1. Ligand's Product Portfolio

Drug	API/mechanism	Indication	Partner
Promacta	Thrombopoietin mimetic	ITP	GSK
Conbriza	SERM	Osteoporosis	Pfizer
Fablyn	SERM	Osteoporosis	Chiva
Nexterone	Amiodarone	Arrhythmia	Baxter Int'l
Cerenia	Canine anti-nausea	Animal Health	Pfizer
VFEND	IV Voraconazol	Antifungal	Pfizer
Abilify - IM	IM-Aripiprazole	Schizophrenia	BMS
Geodon	IV-Ziprasidone	Schizophrenia	Pfizer
Carfilzomib	Proteasome Inhibitor	Oncology	Onyx
Promacta	Thrombopoietin mimetic	Hepatitis C	GSK
Aprela	Conbriza & Premarin	Menopause	Pfizer
Carbamazepine	New version of Tegretol	CNS disorders	Ludbeck
Undisclosed	Undisclosed	Undisclosed	Merck
Promacta	Thrombopoietin mimetic	Oncology	GSK
Dinaciclib	CDK Inhibitor	Oncology	Merck
Navarixin	CXCR2 Antagonist	Oncology/COPD	Merck
BMS 582949	p38 Inhibitor	Atherosclerosis	BMS
Tranzisertib	JNK Inhibitor	Pulmonary Fibrosis	Celgene
Tanaproget	Progesterone antagonist	Contraceptive	Undisclosed
GSK2285921	Thrombopoietin mimetic	ITP	GSK
LGD-4033	SARM	Muscle wasting	Internal
Clopidrogel IV	New version of Plavix	Arrhythmia	Medicine Co.
BACE	β-secretase inhibitor	Alzheimer's disease	Merck
Pradefovir	Hepatitis B inhibitor	Hepatitis B	Chiva
MB07133	Hepatitis B inhibitor	Primary liver cancer	Chiva
XL652	LXR Agonist	Atherosclerosis	Exelixis
XL550	MR Antagonist	Metabolic disorders	Exelixis
Melphalan	New version of Alkeran	Oncology	In-house
Undisclosed	Undisclosed	CNS disorder	Sage



Abbreviations: API, active pharmaceutical ingredient; CDK, cyclin-dependent kinase; CNS, central nervous system; COPD, chronic obstructive pulmonary disorder; CXCR2, chemokine receptor-2; ITP, idiopathic thrombocytopenic purpura; JNK, Jun N-terminal kinase; LXR, liver X receptor; MR, mineralcorticoid receptor; SARM, selective androgen receptor modulator; SERM, selective estrogen receptor modulator

The NDA for carfilzomib has been submitted, but it has not been officially accepted yet.
Source: Ligand Pharmaceuticals

Legend to Table 1:

Novel pharmaceutical agents

Captisol-formulated drugs

NOVEL PHARMACEUTICAL AGENTS

Ligand's portfolio of innovative compounds covers a wide range of therapeutic categories and all phases of development as shown in Table 1. Because of the number of programs based on Ligand-owned compounds, we have included only those on the market or in/near clinical development. Ligand also has one partnered program and three unpartnered programs in preclinical development and more than 10 that are at an earlier stage.

The most recent partnering deal is Chiva's licensing of the worldwide rights to the osteoporosis medicine Fablyn®. That drug was originally under development with Wyeth and was returned to Ligand after Wyeth's acquisition by **Pfizer**, because the new parent already had a similar compound, Conbriza®, under license from Ligand. Chiva intends to launch Fablyn in Europe in the near future, since it is already approved there, and to conduct a bridging study to gain approval in its home country, China, and Japan, probably in the 2013/2014 timeframe. The licensing agreement for Fablyn will generate $4 million over the first 8 months, which started in October. In addition, Ligand will receive milestones and royalties on Chiva's sales.

Other programs have considerably greater profit potential for Ligand, and rather than attempt to summarize each, the next sections of our report focus on two that we believe represent the profit potential of others in the Company's portfolio and portray the breadth of its pipeline.

PROMACTA – AN IMPORTANT SOURCE OF REVENUE GROWTH

The single most important drug in Ligand's portfolio is probably Promacta® (eltrombopag), a small-molecule agonist for the thrombopoietin receptor, that is sold by **GlaxoSmithKline**. The drug has been approved in the United States, Europe, and many other countries for the treatment of idiopathic thrombocytopenic purpura, or ITP, but some off-label use may have begun to drive demand.

Promacta is a small, nonpeptide drug that stimulates platelet formation through its binding to the thrombopoietin receptor and activation of a pathway that promotes the proliferation and differentiation of bone marrow progenitor cells into megakaryocytes, the cells from which platelets are derived. (Platelets are cells required for normal blood clotting.) The original class of compounds was reported in 2001 and subsequent work identified a modified version with improved oral bioavailability.[1,2] Accordingly, the original patent on Promacta expires in 2022, though extensions protect it through 2025. Characterization of the compound found that it interacts only with the thrombopoietin receptor of humans and non-human primates. Moreover, because Promacta and thrombopoietin bind to different sites on the same receptor, their stimulatory effects are additive.[3]

ITP – Promacta's Initial Indication

GlaxoSmithKline has conducted numerous clinical studies to determine how Promacta should be use. The first indication that received regulatory approval is ITP, a bleeding disorder that afflicts 300,000 – 600,000 individuals in the United States.[4,5] This disease is characterized by an immune-mediated destruction of platelets that has no known underlying cause.

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[1] Duffy, KJ, et al. Hydrazinonaphthalene and azonaphthalene thrombopoietin mimics are nonpeptidyl promoters of megakaryocytopoiesis. J Med Chem 2001; 44(22): 3730.
[2] Erickson-Miller, CL, et al. discovery and characterization of a selective, nonpeptidyl thrombopoietin receptor agonist. Exp Hematol 2005; 33(1): 85.
[3] Erickson-Miller, CJ, et al. Preclinical activity of eltrombopag (SB-497115), an oral, nonpeptide thrombopoietin receptor agonist. Stem Cells 2009; 27(2): 424.
[4] Segal, JB and Powe, NR. Prevalence of immune thrombocytopenia: analyses of administrative data. J Thromb Haemost 2006; 4(11): 2377.
[5] Fuedjo-Tepie, MA, et al. Prevalence of diagnosed chronic immune thrombocytopenic purpura in the US: analysis of a large US claim database: a rebuttal. J Thromb Haemost 2008; 6(4): 713.

Promacta is garnering market share overseas, partly because it is an oral medicine taken once daily one hour before or 2 hours after a meal, while **Amgen's** drug Nplate® (romiplostim) must be injected on a weekly basis. (In the United States, Promacta's oral formulation is at a disadvantage, since Medicare pays for all injectables and their administration, while patients incur a copay for oral medicines, including Promacta. Elsewhere, the oral formulation has a clear-cut advantage.) While there are some differences between the drugs' efficacy and safety profiles, a study of patient satisfaction comparing them found that patients who took both drugs preferred Promacta for its convenience and overall treatment satisfaction – otherwise, the patients felt them to be comparable.[6] (Note that Nplate also differs from Promacta in its structure – Nplate is a fusion protein that links a thrombopoietin-like peptide to a portion of an antibody.)

Efficacy Data: Promacta elicits a dose-dependent increase (dose range: 30 mg, 50 mg and 75 mg per day) in platelet counts starting in the second week after initiation of therapy, and the platelet levels achieved with each dose are inversely proportional to the incidence of bleeding episodes that normally accompany ITP.[7] This relationship has been demonstrated in several trials that investigated the efficacy of Promacta over periods of 6 weeks to up to 4.5 years.[8,9,10] These clinical studies also demonstrated that prior treatment with corticosteroids or splenectomy has no effect on the patient's response to Promacta. Moreover, they show that chronic use of the drug is required to effectively treat ITP, since platelet levels return to the patient's baseline value within 1 – 2 weeks after treatment has stopped.

Safety: Clinical studies involving ITP patients have carefully monitored toxicities that might be associated with the therapy, partly because these patients use the drug chronically. Overall, Promacta has a very good safety profile.[11] A meta-analysis of the clinical trials, involving 9,788 patient-weeks, found upper respiratory tract infections (1.1 events per 100 patient weeks), headache (0.8), and fatigue (0.5) to be the three most common non-serious, non-bleeding adverse events. Serious toxicities were also tabulated, and nothing occurred more frequently with the drug than with placebo, when expressed as a percentage of patients treated (range: 3%-8%). Among the potential issues were bone marrow fibrosis, thrombosis, rebound thrombocytopenia, hematologic malignancy, hepatotoxicity, and cataract formation/ progression. When Promacta was used for prolonged periods of up to 4.5 years, no new safety signals were detected, and when the drug was administered to the elderly (patients older than 65), the overall safety profile was not affected by age.[10,12] Thromboembolic events did show an age-related trend (2% in 18-49 year old patients, 3% in the 50-64, and 9% at 65 and older), but that was not entirely unexpected.

Cataracts and bone marrow fibrosis have merited attention in GSK's trials because cataracts were seen in a preclinical model that was tested to assess potential toxicities and bone marrow fibrosis has been considered a theoretical complication of thrombopoietic receptor agonists. Evidence from patients who have used Promacta for up to 3 and 2 years respectively has shown no relationship between the drug and these conditions.[13,14]

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[6] Kuter, DJ, et al. Patient reported outcomes comparison of chronic immune thrombocytopenia (ITP) patients switched to Promacta and Nplate. 53rd Amer Soc Hematol Annual Meeting 2011; Abstract #2220.
[7] Bussel, JB, et al. Eltrombopag for the treatment of chronic idiopathic thrombocytopenic purpura. N Engl J Med 2007; 357(22): 2237.
[8] Bussel, JB, et al. Effect of eltrombopag on platelet counts and bleeding during treatment of chronic idiopathic thrombocytopenic purpura: a randomized, double-blind, placebo-controlled trial. Lancet 2009; 373(9664): 641.
[9] Cheng, G, et al. Eltrombopag for management of chronic immune thrombocytopenia (RAISE): a 6-month, randomized, phase 3 study. Lancet 2011; 377(9763): 393.
[10] Saleh, MN, et al. Safety and efficacy of extended treatment with eltrombopag in adult with chronic immune thrombocytopenia (ITP) from June 2006 to February 2011. 53rd Amer Soc Hematol Annual Meeting 2011; Abstract #3296.
[11] Cuker, A. Toxicities of the thrombopoietic growth factors. Semin Hematol 2010; 47(3): 289.
[12] Olney, HJ, et al. Efficacy and safety of eltrombopag in elderly patients with chronic immune thrombocytopenia: analysis of five clinical trials. 53rd Amer Soc Hematol Annual Meeting 2011; Abstract #3294.
[13] Cooper, N, et al. Rate of cataracts across the eltrombopag clinical studies in patients with chronic immune thrombocytopenia. 53rd Amer Soc Hematol Annual Meeting 2011; Abstract #1164.
[14] Brynes, RK, et al. Evaluation of bone marrow reticulin in patients with chronic immune thrombocytopenic purpura (ITP) treated with eltrombopag – data from the Extend study. 53rd Amer Soc Hematol Annual Meeting 2011; Abstract #528.

A small, separate clinical trial has corroborated a preclinical finding that Promacta does not alter the function or activation status of platelets.[15] In that trial, small groups of ITP patients (6 – 13) received Promacta, steroids, or no treatment and their platelets were evaluated via two markers for adhesion and aggregation. No differences were identified between the groups. This confirmed data from a preclinical study that compared the effect of Promacta and thrombopoietin on platelet function *in vitro.*[16] The experiment determined that the drug has no effect on platelet activation, unlike the endogenous growth factor. That is important because it reduces the risk of thrombotic complications.

Promacta has also been evaluated in healthy subjects to assess its impact on heart function.[17] In all, 48 individuals participated in a double-blind, crossover study that compared two doses of Promacta (50 mg and 150 mg) and a positive control, moxifloxacin. The results showed that five days on Promacta therapy has no effect on cardiac repolarization (i.e. no QTc prolongation). This eliminated a potential risk from consideration during clinical use and a major impediment to regulatory approval.

Expanding the Market to Include Hepatitis C-related Thrombocytopenia

Hepatitis C virus infections are known to cause thrombocytopenia even when hepatic disease is not apparent. Indeed, approximately 20% of patients diagnosed with chronic ITP are seropositive for the hepatitis C virus.[18] Abnormally low platelet counts (in the range of 20,000 – 70,000/μL) render the patient susceptible to serious bleeding episodes. Thrombocytopenia also prevents the patient from receiving antiviral therapy, since pegylated α-interferon treatment reduces platelet counts. (The standard of care today is a cocktail of pegylated α-interferon [pegylated α2a-interferon sold as Pegasys® by Roche and pegylated α2b-interfeon sold as PegIntron® by **Merck**], ribavirin [sold as Rebetrol® by Merck], and recently approved telaprevir [sold as Incivek® by **Vertex**].) What's more, reducing the doses or discontinuing the therapy is the norm for controlling unwanted side effects, such as thrombocytopenia, and both reduce efficacy.[19]

Attempts to treat thrombocytopenia prior to initiation of antiviral therapy met with difficulties before Promacta was approved. Steroids exacerbate the infection, and platelet transfusions are costly and may cause other infections.

Efficacy – Hepatitis C Trials: GlaxoSmithKline has conducted several clinical studies to evaluate the use of Promacta prior to and during antiviral therapy. The two largest trials were dubbed ENABLE 1 and ENABLE 2, which only recently ended. Overall, the data indicate that Promacta is effective in raising platelet counts in hepatitis C patients prior to antiviral therapy and helps to maintain the counts once the antiviral treatment has begun.

A Phase 2 clinical trial established a dose-response relationship between Promacta doses and the proportion of hepatitis C patients capable of remaining on antiviral therapy, as depicted in Figure 2.[20] The primary endpoint was an increase in platelet count from a baseline of 20,000 – 70,000/μL after an initial 4-week treatment phase. Secondary end points pertained to safety, tolerability, and continuation on pegylated interferon therapy during an antiviral treatment phase.

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[15] Haselboeck,J, et al. Platelet function and activation in patients with immune thrombocytopenia treated with eltrombopag: comparison with steroid-treated and untreated patients. 53rd Amer Soc Hematol Annual Meeting 2011; Abstract #3280.
[16] Erhardt, JA, et al. Comparative analyses of the small molecule thrombopoietin receptor agonist eltrombopag and thrombopoietin on in vitro platelet function. Exp Hematol 2009; 37(9): 1030.
[17] Matthys, G, et al. Eltrombopag does not affect cardiac repolarization: results from a definitive QTc study in healthy subjects. Br J Clin Pharmacol 2010: 70(1): 24.
[18] Garcia-Suarez, J, et al. HCV-associated thrombocytopenia: clinical characteristics and platelet l response after recombinant alpha2b-interferon therapy. Br J Haematol 2000; 110(1): 98.
[19] Sung, H, et al. Management of hepatitis C antiviral therapy adverse effects. Curr Hepatitis Rep 2011; 10(1): 33.
[20] McHutchinson, JG, et al. Eltrombopag for thrombocytopenia in patients with cirrhosis associated with hepatitis C. N Engl J Med 2007; 357(22): 2227.

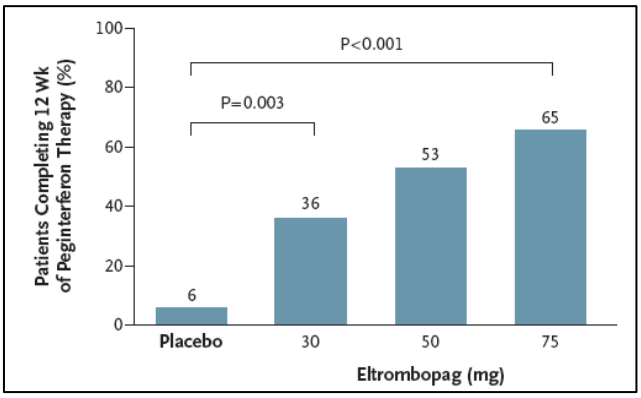


Figure 2. The relationship between Promacta doses and completion of a 12-week course of pegylated α-interferon (Pegasys or PegIntron) was assessed in hepatitis C patients whose platelet counts were <75,000/μL at the baseline. Three doses of Promacta and a placebo were tested. After 4 weeks on Promacta, platelet counts were at a maximum. Patients with platelet counts of ≥100,000/μL received interferon and Promacta treatment was continued throughout the antiviral therapy. The chart shows a strong relationship between the Promacta dose and the percentage of patients able to complete the 12-weeks of interferon.

Source: McHutchison, JG, et al. [20]

Two Phase 3 studies extended this work to larger patient populations. Both enrolled individuals with chronic hepatitis C infections and cirrhosis whose baseline platelet counts were <75,000/μL, rendering them ineligible for antiviral therapy. The ENABLE 1 trial used Roche's Pegasys plus ribavirin, while the ENABLE 2 trial used Merck's PegIntron and ribavirin. (Note that these clinical trials were initiated before Vertex's telaprevir was approved.) In both studies, patients received Promacta with an escalation in Promacta doses that started at 25 mg daily and were adjusted every two weeks up to 100 mg or until the platelet counts were ≥90,000/μL for Pegasys and ≥100,000/μL for PegIntron (in accordance with the drugs' labels). The primary endpoints were identical – a sustained viral response rate as defined as the percentage of subjects with non-detectable hepatitis C virus-RNA at 24 weeks post-completion of the planned treatment period (i.e., week 48 for virus genotype 2/3 or week 72 for non-genotype 2/3). Both trials also had the same secondary outcome measures, the proportion of subjects who achieved a shift in platelet count from <75,000/μL to within the treatment ranges for each interferon, adverse events, lab abnormalities, ocular examination findings, 12-lead ECGs, and information from clinical monitoring. Inclusion and exclusion criteria were identical in the two trials.

Data from the ENABLE 1 study was presented at the 2011 meeting of the American Association for the Study of Liver Disease on November 7th.[21] Of the original 717 patients enrolled, 68% had cirrhosis, 62% were male, and 17% were of Japanese/East Asian ancestry. The results showed that treatment with Promacta increased the median baseline platelet levels from 59,000/μL to 89,000/μL by week 2. This rendered 95% or 682 patients enrolled in the first phase of the study eligible for antiviral therapy. In the second phase, the eligible patients were divided into two groups, a control group that no longer received Promacta and the treated group that continued to receive it. Both were then treated with Pegasys (180 μg/week) and ribavirin (genotype 2/3: 800 mg daily; non-genotype 2/3: 1200 mg/day or 1000 mg if their body weight was below 75 kg). As shown in Figure 3, 23% patients who received continuous Promacta therapy had a sustained viral response, versus 14% who only received it in the first phase of the trial. Not surprisingly, continuous Promacta treatment was associated with a delay in the interval to the first antiviral dose reduction and with a smaller proportion of antiviral dose reductions. The primary endpoint of ENABLE 1 was met – Promacta significantly improved the sustained viral response to antiviral therapy by patients with advanced liver disease. Top-line data from the ENABLE 2 trial that was recently released has corroborated the ENABLE 1 results.

[21] Afdhal, N, et al. Final results of ENABLE 1, a phase 3, multicenter study of eltrombopag as an adjunct for antiviral treatment of hepatitis C virus-related chronic liver disease associated with thrombocytopenia. AASLD 2011 Annual Meeting Abstract #LB-3.

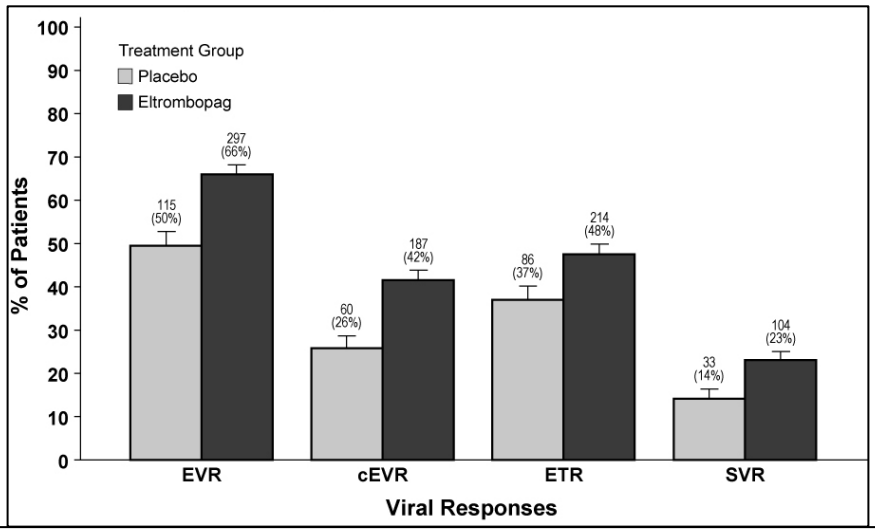


Figure 3. Patients in the ENABLE 1 trial who received continuous Promacta therapy (■) had better response rates to Pegasys and ribavirin than those who received treatment for their pre-existing thrombocytopenia only prior to the antiviral drugs (□). Viral responses were assessed at four different times: EVR, early viral response (undetectable HCV-RNA or a ≥2 log decline in HCV-RNA after 12 weeks of treatment); cEVR, complete early viral response; ETR, end of treatment response; and SVR, sustained viral response, which was measured 24 months after treatment ended. Note that EVR, cEVR, and ETR are useful for monitoring a patient's progress, while SVR was the primary endpoint of the ENABLE 1 trial.

Source: Afdhal, N, et al. [21]

Safety – Hepatitis C Trials: Results from the Phase 2 clinical trial found no unusual side effects related to Promacta therapy. The most common side effects were headache, dry mouth, abdominal pain, and nausea. Given the small number of patients, a relationship between the Promacta dose and the observed side effects could not be established.

The ENABLE 1 trial confirmed the safety results from the earlier study, as headache (7%), fatigue (4%), nausea (3%), and diarrhea (3%) were the most common.[22] Thromboembolic events occurred with the same frequency (2%) in the Promacta and placebo groups. We note that this side effect has been observed in 1%-2% of treated patients, according to the drug's label. Other circulation-related events, such as retinal vein thrombosis, deep vein thrombosis and portal vein thrombosis, were infrequent and/or well balanced between the placebo and Promacta groups.

Top-line safety data from the ENABLE 2 study was discussed at a November 7th presentation on ENABLE 1 at the American Association for the Study of Liver Disease. The intended message was that there is a preliminary safety signal from ENABLE 2 that needs further investigation to understand its true meaning. Based on how Ligand's shares traded the next day, it seems the investment community's interpretation was that the risks associated with gaining regulatory approval and market acceptance for hepatitis C patients is greater because of ENABLE 2. We disagree with the investment community's interpretation of the preliminary safety data. As discussed above, there is a large amount of information from other trials that have yielded a consistent side effect profile for Promacta. Moreover, cirrhosis is a pro-thrombotic condition and many of the thrombotic events in the ENABLE 2 trial were asymptomatic and discovered only through the extensive testing (e.g., ultrasonography) that the study required.[23] Finally, we note adverse events reported from the patients receiving continuous Promacta weren't that

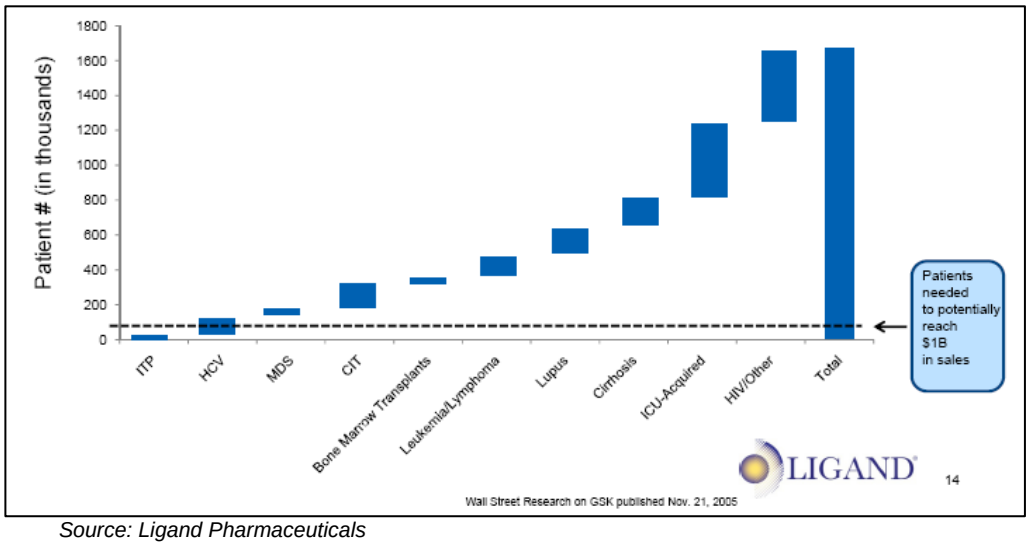
[22] Dusheiko, G, et al. Final results of open-label treatment with eltrombopag during ENABLE 1: A study of eltrombopag as an adjunct for antiviral treatment of hepatitis C virus associated with thrombocytopenia. 53rd Amer Soc Hematol Annual Meeting 2011; Abstract #2232.
[23] ENABLE 1 Panel Discussion, November 7, 2011.

unusual – rather, the placebo group was slightly abnormal, as there were no thrombotic events reported from that group. According to two investigators who participated in the ENABLE 1 and 2 studies, the thrombotic safety signal of ENABLE 2 would not exist if the placebo patients had the expected rate of thrombosis.[23]

Promacta's Potential Markets & Ligand's Future Royalties

ITP and thrombocytopenia caused by chronic hepatitis C infections are only two indications for which Promacta may have benefit, since dangerously low platelet levels are associated with other conditions. Figure 4 provides a breakdown of the other indications and the relative sizes of the patient populations.

Figure 4. The Multiple Submarkets of Thrombocytopenia-Inducing Diseases



Source: Ligand Pharmaceuticals

ITP is a relatively small market opportunity, while hepatitis C appears to be one of moderate size. GlaxoSmithKline hasn't revealed its development strategy for Promacta beyond hepatitis C, but new initiatives are under way as shown in Table 2.

Table 2. New Clinical Trials Involving Promacta

Indication	Study Phase	Est'd Completion
Solid tumors treated with gemcitabine ± carboplatin or cisplatin	2	Sept 2013
MDS or AML	2	Oct 2012
MDS treated with hypomethylating agent	1/2	Feb 2013
CLL	1/2	June 2013
CLL	2	Nov 2013
CML treated with Imatinib or similar drug	2	Jan 2015

Source: ClinicalTrials.gov website accessed 11/15/2011

These initiatives are based on preclinical studies that suggest the drug will be safe and effective in treating patients with these diseases.[24] An examination of thrombopoietin receptor mRNA found in tumor cell lines and primary tumors determined that the receptor to which Promacta binds is either undetectable or is expressed at very low levels. Out of 355 tumor cell lines, only three expressed mRNA for the receptor above the normal range; these were one lung tumor and two erythroleukemia lines. In addition, primary prostate, lymphoma, and colon tumors failed to express the thrombopoietin receptor mRNA at

[24] Erickson-Miller, CL, et al. Thrombopoietin receptor levels in tumor dell lines and primary tumors. J Oncol 2010; 135354: 1.

measurable levels. A separate study examined the effect of Promacta on proliferation, apoptosis, differentiation, colony formation, and malignant self-renewal of bone marrow mononuclear cells taken from patients with myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML).[25] The results indicate that the drug, at concentrations over the range of 0.1 – 30 µg/mL, did not stimulate proliferation or colony formation by malignant cells in culture and did not decrease apoptosis or facilitate tumor engraftment when the cells were implanted as xenografts. However, Promacta did function as expected in stimulating normal megakaryocyte colony formation from cells derived from MDS and AML patients. Combined, these preclinical studies support the safety of Promacta for patients with a precancerous condition, MDS, hematological malignancies, and at least some solid tumors, while also providing early data on efficacy.

Based on the latest clinical trials, it seems that GlaxoSmithKline will pursue myelodysplastic syndrome (MDS) and/or a hematological malignancy in its next step to expand Promacta's commercial market. What this means to Ligand Pharmaceuticals can be appreciated from Table 3.

Table 3. Promacta Tiered Royalty Rates ⧗

Promacta Royalty

Annual Sales	Royalty
<$100M	4.70%
$100M-$200M	6.60%
$200M-$400M	7.5%
$400M-$1.5B	9.40%
>1.5B	9.30%

Illustrative Ligand Revenue

Annual Sales	Blended Royalty	Ligand Revenue
$500M	7.1%	$36M
$1B	8.3%	$83M
$1.5B	8.6%	$130M

⧗ Net royalty rates due Ligand after payment to Rockefeller University
Source: Ligand Pharmaceuticals

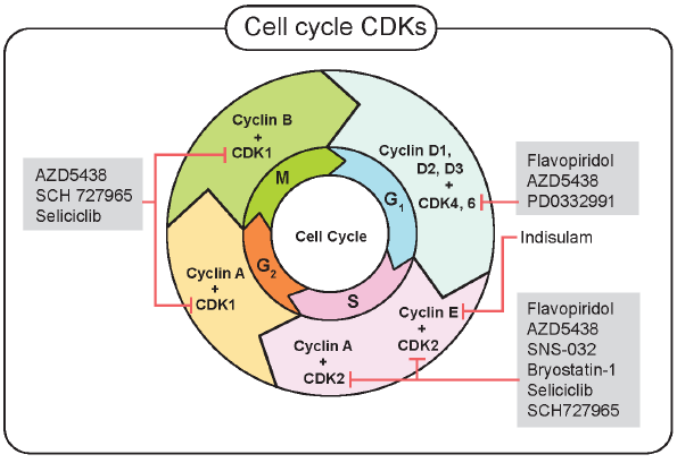
The royalties that Ligand receives on Promacta sales are determined by the tiered royalty rate structure shown on the left side of the table. The rate increases in steps from 4.7% on the first $99.9 million of sales to 9.4% on sales between $400 million and $1.5 billion. Above $1.5 billion in sales, the rate is 9.3%. The blended rates are presented on the right side of the table, which shows that Ligand will receive $36 million in royalties on $500 million of Promacta sales and $83 million on $1 billion of sales. Thus, Ligand benefits from increases in the volume of business and higher royalty rates up to $1.5 billion of sales.

[25] Will, B, et al. Effect of the nonpeptide thrombopoietin receptor agonist Eltrombopag on bone marrow cells from patients with acute myeloid leukemia and myelodysplastic syndrome. Blood 2009; 114(18): 3899.

DINACICLIB – A NEW CANCER THERAPY

Dinaciclib is at an earlier stage of clinical development than Promacta, but it's unique properties may warrant its approval sooner than many oncology drugs. The compound is an orally available, small molecule inhibitor of cyclin-dependent kinases (CDKs) that play important roles in governing the transitions from the S phase of the cell cycle to the G_2 phase and into the M phase. These phases of the cell cycle are periods in which the cell first prepares for division by replicating its DNA and then by checking that all is prepared for the next step, which is mitosis (i.e., cell division) in the M phase. The cell cycle is diagrammed in Figure 5, which includes some of the steps at which dinaciclib (SCH 727965) acts.[26]

Figure 5. The Cell Cycle & Dinaciclib's Targets [26]



This figure provides a highly simplified version of the participants governing the cell cycle. For instance, there are numerous cyclins and at least 9 CDKs, as well as endogenous inhibitors that control the kinases' activities. Targeting this regulatory system as an approach to treating cancer makes sense for a couple of reasons. First cancer is a disease noted for uncontrolled cell proliferation. Hence, an inhibitor(s) that blocks a cell's progression through the cell cycle may be capable of slowing or halting the unrestrained growth, and that may move the cell toward apoptosis. The other reason for targeting this regulatory system is because some cancers are noted for overexpressing certain cyclins, such as cyclin D2 in chronic lymphocytic leukemia.[27] Several drug candidates have been developed to target CDKs, as shown in the diagram, but dinaciclib is unique based on several important traits.

Preclinical Activity Points to Multiple Clinical Applications

Dinaciclin inhibits CDK1, CDK2, CDK5, and CDK9 at concentrations in the range of 1 – 4 nmol/L, while having little/no effect on many other tyrosine kinases.[28] A short exposure to the compound has lasting effects on cell function, including suppression of DNA synthesis and induction of cell apoptosis in the G_1 phase. This suggests that continuous exposure may not be required for sustained activity *in vivo.* A study of its mechanism of action found that it induces apoptosis by concomitantly inhibiting CDK1 and CDK2 and by altering mitochondrial integrity, resulting in the release of cytochrome c.[29] The result is an increase in apoptosis during the G_1 phase, perhaps because CDK2 promotes entry into the S phase and CDK1 helps to move the cell through the S phase and into the M phase.

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[26] Dickson, MA and Schwartz, GK. Development of cell-cycle inhibitors for cancer therapy. Cur Oncol 2009; 16(2): 36.
[27] Igawa, T, et al. Cyclin D2 is overexpressed in proliferation centers of chronic lymphocytic leukemia/small lymphocytic lymphoma. Cancer Sci 2011; 102(11): 2103.
[28] Parry, D, et al. Dinaciclib (SCH 727965), a novel and potent cyclin-dependent kinase inhibitor. Mol Cancer Ther 2010; 9(8): 2344.
[29] Fu, W, et al. The cyclin-dependent kinase inhibitor SCH 727965 (dinaciclib) induces the apoptosis of osteosarcoma cells. Mol Cancer Ther 2011; 10(6): 1018.

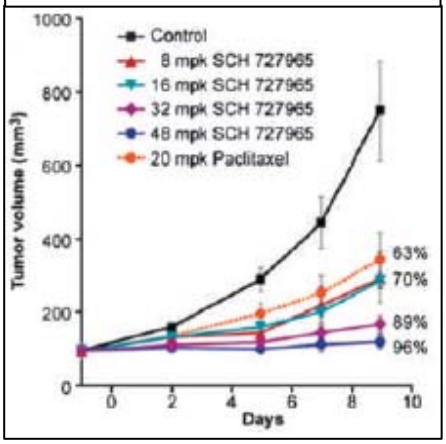
As shown in Table 4, dinaciclib is able to inhibit cell proliferation of a broad range of malignant cells, and it did so at concentrations that can be achieved clinically.

Table 4. Dinaciclib Is Active Against a Wide Variety of Solid and Hematological Cancers [28]

Tumor cell line	Mean in-cell IC_{50} (clonogenicity; nmol/L)	Detectable caspase activation* (single exposure)
Prostate	12	4 of 5
Breast	8	6 of 7
Colon	17	5 of 9
SCLC	14	8 of 9
SCLC	6	2 of 6
Ovarian	14	5 of 7
Pancreatic	15	11 of 15
Melanoma	9	9 of 9
Leukemia	6	5 of 6
Bladder	10	1 of 2
Liver	8	2 of 2
Mantle cell lymphoma	7	3 of 4
Lymphoma (NHL)	7	8 of 8

Abbreviations: SCLC, small-cell lung cancer; NHL, non-Hodgkin lymphoma.
*Data indicate the number of caspase-positive cell lines out of total number of cell lines from each tumor cell line type tested.

Figure 6. Dose Response Relationship of Dinaciclib Compared with Paclitaxel [28]



Preclinical testing also found that the compound is well tolerated at doses that are therapeutically important. Indeed, growth of ovarian cancer xenografts was nearly completely inhibited at a dose well below the maximum tolerated dose (MTD) of 60 mg/kg. (See Figure 6.) A comparison of the inhibitory activities of dinaciclib and paclitaxel shows that the latter inhibited tumor growth by 63% at a dose (20 mg/kg) equivalent to 50% of its MTD, while tumor growth was inhibited by 90% at approximately 53% dinaciclib's MTD. A separate study with osteosarcoma cells found that dinaciclib is effective at concentrations 1,000-fold and 10-fold lower than those required with two other CDK inhibitors under development, flavopiridol (**Sanofi's** alvocidib) and roscovitine (**Cyclacel Pharmaceutical's** seliciclib). We note, too, that it works effectively in combination with another anticancer therapy. A preclinical study that tested dinaciclib and gemcitabine determined that the combination was more effective in inhibiting growth of pancreatic cancer xenografts than either compound was alone.

Early Clinical Data Support Further Development

Thus far, the several clinical trials that have been conducted with dinaciclib have been small Phase 1 or Phase 1/2 studies that were used to learn about its side effect profile, determine a MTD in humans, and gain information about dosing regimens for different cancers. Accordingly, the studies have moved the drug's development forward, while yielding some encouraging but not statistically meaningful data on efficacy.

One indication that is attracting attention is chronic lymphocytic leukemia (CLL). Merck recently secured Orphan Drug designation for this disease, which strikes about 12,300 individuals annually in the United States. Still, it is the most common type of leukemia and one that has not shown improvement in survival in the past decade. A Phase 1 trial tested doses of 5, 7, 10, 14, and 17 mg/m^2 in 33 patients with

relapsed/refractory CLL.[30] The drug was administered as a 2-hour infusion on days 1, 8, and 15 of a 28 day cycle, and the MTD was determined to be 14 mg/m^2. Dinaciclib is rapidly eliminated, with a half life of approximately 3 hours. The median number of cycles administered was 5, though 9 patients had 6-8 cycles and 5 patients, 10-16 cycles. There were 15 partial responses, enabling 4 patients to receive potentially curative stem cell therapy. Common side effects included neutropenia, anemia, thrombocytopenia, hyperglycemia, hypocalcaemia, elevated serum transaminase, diarrhea and leucopenia. In all, the drug is considered to have an acceptable safety profile, though a modified dosing regimen that starts at 10 mg/m^2 followed by 14 mg/m^2 is being tested to avoid tumor lysis syndrome, which occurred in the study.

Dinaciclib has also been tested in patients with other hematological malignancies, including advanced acute myeloid and lymphoid leukemias, diffuse large cell lymphoma, and low grade lymphoma. The drug regimen used to treat the advanced leukemias was a single dose 50 mg/m^2 administered as a 2-hour infusion once every 21 days. The lymphoma patients received the drug regimen employed in the CLL study. Anticancer activity was apparent, with 60% of the leukemia patients responding with lower circulating blast counts (10 with >50% decrease and 6 with >80% drop) and with smaller tumor masses in the lymphoma patients (range: 8% – 85%). Six patients in the leukemia trial experienced tumor lysis syndrome after the initial dose. Otherwise, the side effects were not that different from those identified in the CLL trial.

Patients with advanced solid tumors have also been treated with dinaciclib. The most recent tested two different infusion regimens: One part of the study was conducted to establish a 2-hour infusion regimen and 50 mg/m^2 was determined to be acceptable, while the second part employed 8 and 24 hour continuous infusions, with 7.4 and 10.4 mg/m^2 being well tolerated. No objective responses were noted, though 10 patients in the latest trial achieved stable disease for 6 – 30 cycles. In an earlier study, PET scans identified a reduction in tumor metabolic activity of as much as 30+%.

At this juncture, Merck has one new trial enrolling patients – it will evaluate different doses of dinaciclib for hematological malignancies (i.e., non-Hodgkin's lymphoma, malignant myeloma, and CLL). This Phase 1 study is expected to end in November 2012. Two other trials are also under way: The Dana Farber Cancer Institute is examining dinaciclib in combination with veliparib $\pm$ carboplatin for patients with advanced solid tumors, and it has a malignant melanoma Phase 1/2 trial that is designed to optimize the dose and evaluate overall survival at one year.

Based on the data from the trials conducted to date and the Orphan Drug status for CCL, we look for Merck to initiate more advanced studies in the coming year and for the drug to be launched in 2015. Dinaciclib will generate mid-single-digit royalties for Ligand, much like another drug, navarixin, that Merck is developing. (Navarixin is a novel therapy that is being developed for conditions with an inflammatory element to their etiologies. The compound is a CXCR-2 antagonist that has shown high selectivity for neutrophils and an ability to thereby halt/prevent inflammation.)

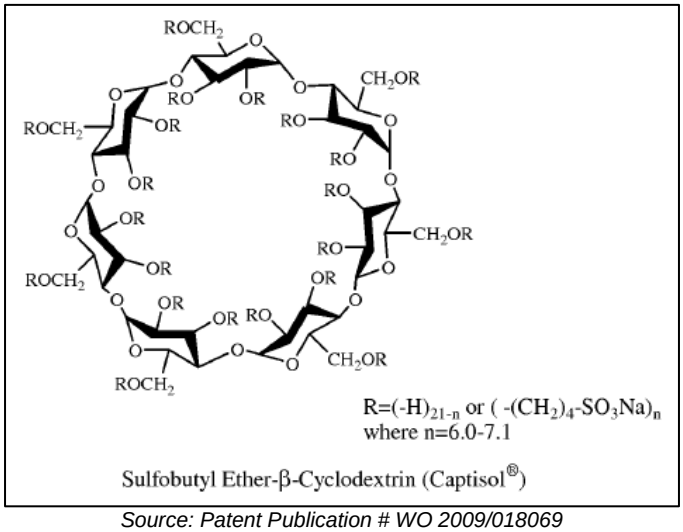
[30] Flynn, JM, et al. Phase I study of the CDK inhibitor dinaciclib (SCH 727965) in patients with relapsed/refractory CLL. J Clin Oncol 2011; 29 (suppl): Abstract 6623.

THE CAPTISOL PLATFORM

Ligand acquired a privately owned company called CyDex Pharmaceuticals on January 26, 2011. The $35.5 million deal greatly expanded Ligand's product portfolio with the addition of more than 25 programs, including five FDA approved drugs, and gave the Company rights to the excipient Captisol®.

Captisol is a β-cyclodextrin, which is a cyclical molecule composed of seven dextrose sugar rings that are modified by attachments as shown in Figure 7.

Figure 7. Structure of Captisol



Source: Patent Publication # WO 2009/018069

Captisol is just one of a great number of such compounds that have been used by the pharmaceutical and food industries for years. The reason the drug industry has a particular interest in this family of molecules is because they have the ability to form inclusive complexes with drugs and thereby alter various properties of the active pharmaceutical ingredient.[31] A simple schematic diagram of this interaction is presented in Figure 8.

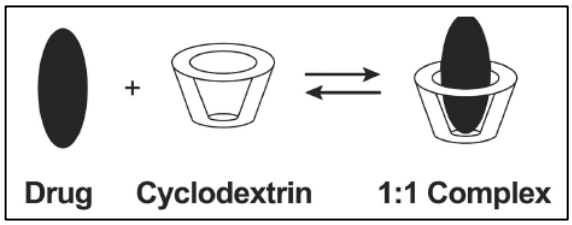


Figure 8. A schematic diagram depicts the formation and disassociation of the inclusive complex between a drug and a cyclodextrin molecule.

Source: Stella, VJ and He, Q. [31]

Envelopment of the drug by cyclodextrin alters the solubility of the pharmaceutical agent, which may result in better solubility and pharmacokinetic properties, depending on the chemical moieties attached to the dextrose rings (see Figure 7). The two most common uses of a cyclodextrin are to improve the active ingredient's solubility and to minimize injection-site damage or irritation. Ligand's Captisol is one of only two cyclodextrin excipients approved by the FDA for pharmaceutical use. (The other, hydroxypropyl- β-cyclodextrin, was developed by the Janssen Pharmaceutical segment of **Johnson & Johnson**.) Four of Ligand's FDA-approved drugs formulated with Captisol are basic compounds and the presence of the excipient maintains the active ingredients in solution at a physiological pH. In addition, it also prevents injection-site problems for the three that are injectable products.

[31] Stella, VJ and He, Q. Cyclodextrins. Toxicol Pathol 2008; 36(1): 30.

Captisol does not readily cross membranes, so oral administration does not result in meaningful systemic exposure. Moreover, following intravenous administration, the excipient is rapidly excreted unmetabolized from the kidney. This probably contributes to its excellent safety profile, which has been demonstrated in more than 100 clinical trials. There are currently 5 FDA-approved drugs that use Captisol and another 6 that are in or about to enter clinical testing, as shown in Table 1. In addition, Ligand has 25 more, undisclosed programs under development with partners that utilize Captisol.

Several of the early drugs that were developed under partnerships between CyDex and larger pharmaceutical companies have a relatively low volume of sales and a few are going to lose patent protection in the near future. Yet, it is important to note that more than 100 customers order Captisol.

The latest Captisol deal, which was announced on October 19th, is with Sage Therapeutics, a privately owned pharmaceutical company that specializes in developing drugs to treat various maladies affecting the central nervous system. The agreement covers several compounds, none of which have been disclosed. Ligand believes at least one will enter clinical trials in 2012.

Another undisclosed program is with Merck & Company. Captisol has been used to create an intravenous formulation of a medicine that is currently sold in tablet form. The new preparation should expand the market, quicken the drug's action, and eliminate such issues as variable absorption from the gastrointestinal tract that occur with oral drugs. Ligand has not revealed how quickly the drug might begin to generate commercial sales of Captisol, but for now, it is requiring a supply of the excipient to support the clinical trial. Based on its involvement in a Phase 3 trial, we estimate the drug will launch in 2013.

Another drug, **Onyx Pharmaceuticals'** carfilzomib, might be the next Captisol-enabled product to win FDA approval. The compound is a second-generation proteasome inhibitor that has tested well against multiple myeloma in clinical trials. (Indeed, the company submitted an NDA based on its Phase 2 data and it is conducting two Phase 3 clinical studies, one of which should have data available in the second half of 2012. In addition, the FDA has allowed Onyx to make carfilzomib available to relapsed/refractory multiple myeloma patients under an expanded access program, and it has granted the drug "fast track" status. ("Fast track" status means that the FDA believes carfilzomib fulfills an unmet medical need and that it will review the NDA within 6 months of its filing.) We believe the drug has blockbuster potential and have assumed it wins FDA approval in early 2013.

We think two other drugs serve as good examples of how Captisol technology makes a difference in drug formulations and to healthcare providers and patients.

NEXTERONE – CAPTISOL IMPROVES DRUG SOLUBILITY & SAFETY PROFILE

Nexterone is a patented formulation of amiodarone, a medicine that was approved in tablet form by the FDA 1985 for the treatment of cardiac arrhythmia and as an intravenous formulation in 1995. The drug is a first-line therapy for terminating ventricular arrhythmia and preventing the recurrence of ventricular tachycardia/ventricular fibrillation. However, until Nexterone was launched in mid-June by **Baxter International**, intravenous amiodarone preparations were formulated only as a concentrate stabilized in polysorbate 80 and benzyl alcohol. These additives maintain the drug in solution, but they are known to cause hypotension in up to 26% of patients, which can necessitate a slowing of the rate of infusion and may require drug therapy to treat their side effects.[32] What's more, the traditional preparation has had to be filtered and diluted in either a glass or polyolefin bottle for infusions lasting more than 2 hours, because amiodarone's adherence to polyvinyl chloride reduces its concentration in solution and because polysorbate 80 leaches plasticizers from polyvinyl chloride. The need to prepare the drug just prior to use creates an opportunity to introduce errors and it adds to the overall cost of the therapy. Finally, polysorbate 80 interferes with the performance of certain automated infusion delivery systems.

[32] Scheinman, MM, et al. Dose-ranging study of intravenous amiodarone in patients with life-threatening ventricular tachyarrhythmias. The intravenous amiodarone multicenter investigators group. Circulation 1995; 92(11): 3264.

Nexterone has none of these drawbacks. Captisol stabilizes amiodarone in a solution that is ready for use, and it does not appear to cause the hypotension that is associated with the older formulation's solubilizers.[33] Figure 9 compares the effects a loading dose (2.14 mg/kg) and maintenance dose (0.14 mg/kg/min) of Nexterone versus the older amiodarone formulation on the mean aortic blood pressure of dogs.

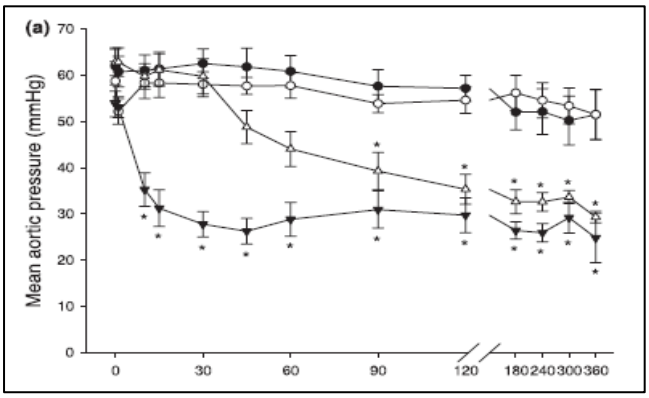


Figure 9. A comparison of the effects of Nexterone and the traditional i.v. formulation of amiodarone on aortic blood pressure in dogs. Three preparations of amiodarone and a control solution (5% dextrose) were studied. The traditional preparation of amiodarone in polysorbate 80 and benzyl alcohol was administered in a loading and maintenance dose (-▼-) or only in a maintenance dose (-△-). Both caused a significant drop in blood pressure when compared with the control (-●-). Nexterone (-○-) administered as loading and maintenance doses had no effect on blood pressure.

Source: Cushing, DJ et al. [33]

Further examination of the effects of Nexterone on cardiac function in a preclinical model found that the hypotension associated with the polysorbate 80/benzyl alcohol preparation was attributable to a decrease in cardiac output.[34] This was accompanied by an increased heart rate. In contrast, Nexterone has no effect on cardiac output or heart rate.

Clinical studies have confirmed the advantages of Nexterone seen in preclinical research versus the traditional amiodarone formulation.[35] Notably, the intravenous formulation did not cause hypotension in an 88-patient study, while it was bioequivalent to the traditional preparation for treating ventricular arrhythmia.[36] Adverse events observed in subjects administered Nexterone were only related to the active ingredient, amiodarone.

Nexterone is sold in two i.v. preparations – 150 mg in 100 mL is available as a 10 minute loading dose (price: $547.92) and 360 mg in 200 mL is offered as a subsequent loading and maintenance therapy (price: $608.80). These ready-to-use preparations can be stored at room temperature with a 2-year shelf life. Thus, Nexterone eliminates the potential for compounding errors that may occur with the traditional formulations and it makes the drug readily available for emergency use.

The size of the patient population for Nexterone is defined largely by the incidence of cardiac arrhythmias outside of a hospital, which is similar in North America, Europe, and Australia (mean: 99.1 per 100,000 persons per year; range: 86.4 – 112.9).[37] Further, the drug is indicated for ventricular fibrillation, which is the initial indication in approximately 34% of the cases. (The reported incidence rate, frequency of ventricular fibrillation and survival differ in Asia from other parts of the world for reasons unknown.) Given the prices of the two Nexterone preparations and the likelihood that more than one maintenance dose will be used on the average patient, we estimate that the market for the drug in the United States and Europe is $350 million.

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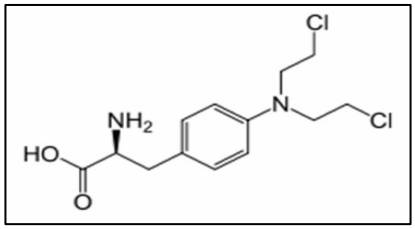
[33] Cushing, DJ, et al. The hypotensive effect of intravenous amiodarone is sustained throughout the maintenance infusion period. Clin Exp Pharmacol Physiol 2010; 37(3): 358.
[34] Cushing, DJ, et al. PM101: a cyclodextrin-based intravenous formulation of amiodarone devoid of adverse hemodynamic effects. Eur J Pharmacol 2009; 607(1-3): 167.
[35] Van Herendael, H. Amiodarone for the treatment and prevention of ventricular fibrillation and ventricular tachycardia. Vasc Health Risk Manag 2010; 6: 465.
[36] Cushing, DJ, et al. Comparative bioavailability of a premixed, ready-to-use formulation of intravenous amiodarone with traditional admixture in healthy subjects. J Clin Pharmacol 2011; e-pub ahead of print January 21, 2011.
[37] Berdowski, J, et al. Global incidences of out-of-hospital cardiac arrest and survival rates: systematic review of 67 prospective studies. Resuscitation 2010; 81(11): 1479.

Baxter acquired Prism Pharmaceuticals, which received a patent on Nexterone in 2005, for $338 million, of which $170 million was paid upon consummation of the deal and $168 million will be due upon achieving certain milestones. Ligand will receive royalties at a rate below 5% on Baxter's sales, and it will book sales of Captisol supplied to prepare the final product. Given Nexterone's competitive advantages and the fact that it has been on the market for little more than 3 months, we believe it constitutes a meaningful near-term growth vehicle for Ligand.

MELPHALAN – CAPTISOL SIMPLIFIES USE & IMPROVES DRUG ADMINISTRATION

Ligand is developing a Captisol version of the oncology drug melphalan to improve upon the original version, which is sold by GlaxoSmithKline as Alkeran®. (See Figure 10.) That drug is an alkylating agent that is commonly used to treat multiple myeloma and in a myeloablative drug regimen to prepare a patient for an autologous stem cell transplant. Yet, it has limited solubility in aqueous solution and is chemically unstable. As a result, an intravenous formulation of Alkeran must be prepared from freeze-dried powder shortly before use in diluents containing propylene glycol. The solubilizer is not ideal, as it is known to cause serious side effects and Alkeran's two-vial preparation system is not convenient.[38]

Figure 10. Melphalan



Early research into the use of Captisol tested two ways to use the excipient.[39] In one, melphalan was prepared as a solution in which the excipient replaced the propylene glycol-based diluent. In the other, Captisol was added prior to the freeze-drying process, so that reconstitution was simplified to a single vial. Both approaches demonstrated that Captisol could replace the Alkeran diluent and that the shelf-life of the reconstituted melphalan was greatly extended. Subsequently, the pharmacokinetic properties of the Captisol-melphalan formulation were tested in a preclinical model, and the results demonstrated that the new version exhibited the same half-life, volume of distribution, and extent of renal elimination as the FDA-approved drug.[40] This suggested that the new preparation could be clinically useful.

When melphalan is used in a myeloablative drug regimen, it is administered at a dose of 180 – 200 mg/m^2, which is a challenge to prepare given the limited solubility. The Captisol formulation was created specifically to address this need. The lead indication is as a myeloablative therapy for multiple myeloma patients who are going to receive an autologous stem cell transplant, which is now the standard of care for patients younger than 65 and capable of undergoing the drug-transplant regimen. However, the disease is age-related, as more than half of new cases are diagnosed in individuals older than 70. And while there has been progress in treating multiple myeloma, prevalence is estimated to be only a little more than 53,000 in the United States.[41] Accordingly, the FDA granted the Captisol-melphalan formulation Orphan Drug status.

Results from a Phase 2a clinical trial, which were reported at the 2011 meeting of the American Society of Clinical Oncology, show that the Captisol formulation produced slightly higher systemic exposure to

[38] Wilson, KC, et al. Propylene glycol toxicity: a severe iatrogenic illness in ICU patents receiving IV benzodiazepines. Chest 2005; 128(3): 1674.
[39] Ma, DQ, et al. New injectable melphalan formulations utilizing (SBE)(7m)-beta-CD or HP-beta-CD. Int J Pharm 1999; 189(2): 227.
[40] Koltun, M, et al. Preclinical comparison of intravenous melphalan pharmacokinetics administered in formulations containing either (SBE)7m-β-cyclodextrin or a co-solvent system. Biopharm Drug Dispos 2010; 31(8-9): 450.
[41] DeVita, Hellman and Rosenberg's Cancer: Principles and Practice of Oncology, Publ by Wolters Kluwer.

melphalan (110%) than Alkeran.[42] (See Figure 11.) The complete pharmacokinetic analysis showed that the two drugs are bioequivalent. Moreover, Alkeran and Captisol-melphalan had a common side-effect profile.

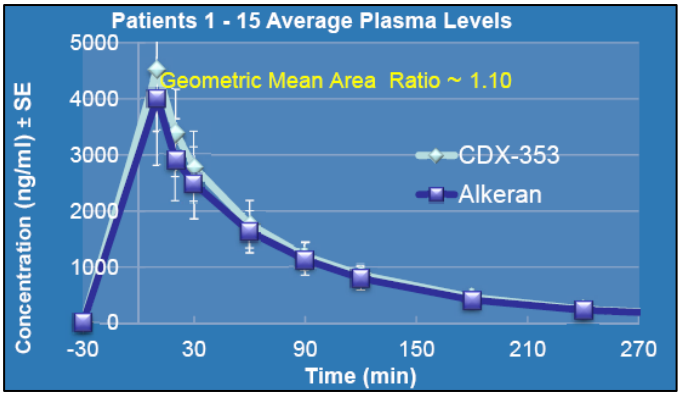


Figure 11. A comparison of melphalan concentrations reached in circulation with the Captisol-melphalan formulation (CDX-353) and with Alkeran. The maximum concentration and the area under the curve obtained with CDX-353 were 110% of those achieved with Alkeran.

Source: Aljitawi, OS, et al.[12]

Ligand intends to follow its practice of seeking partners to complete the development of its melphalan formulation, as it has for its many other programs. At this juncture, discussions have begun with pharmaceutical companies in the United States and abroad, but the timing of a deal is impossible to estimate with any certainty. However, U.S. rights alone should have appeal, as the market generates about $85 million in annual sales. But then, the improved formulation may well command a higher price, and it may help to expand the drug's use beyond multiple myeloma to include other hematological malignancies that are being treated with stem cell transplants.

[42] Aljitawi, OS, et al. Interim results of a Phase IIa, open-label, randomized, pharmacokinetic comparative, cross-over study of melphalan HCl for injection (propylene glycol-free) and Alkeran for injection for myeloablative conditioning in multiple myeloma patients undergoing autologous transplantation, Abstract # 6571. Presented at the 2011 ASCO Annual Meeting, June 2011.

INVESTMENT CONCERNS AND RISKS

For a complete description of risks and uncertainties related to Ligand's business, see the "Risk Factors" section in Ligand's SEC filings, which can be accessed directly from the SEC Edgar filings at www.sec.gov. Potential risks include:

- **Stock risk and market risk:** There is a limited trading market for the Company's common stock. There can be no assurance that an active and liquid trading market will develop or, if developed, that it will be sustained, which could limit one's ability to buy or sell the Company's common stock at a desired price. Investors should also consider technical risks common to many small-cap or micro-cap stock investments, such as float, risk of dilution, dependence upon key personnel, and the strength of competitors that may be larger and better capitalized.
- **New and rapidly changing field:** The pharmaceutical and biotechnology markets are rapidly evolving, and research and development are expected to continue at an accelerated pace. Other companies are also actively engaged in the development of therapies to directly or indirectly treat disorders being pursued by Ligand and its partners. Those companies may have substantially greater research and development capabilities, as well as significantly greater marketing, financial, and human resources abilities.
- **Products still in development phases:** Product development costs and timelines can vary significantly for each product candidate and are difficult to accurately predict. In addition, products in development that appear to be promising may not reach commercialization for various reasons, including failure to achieve regulatory approvals, safety concerns, and/or the inability to be manufactured at a reasonable cost. While Ligand's risk related to individual products in its R&D pipeline may be limited, decisions by partners to terminate development of certain licensed compounds has led the Company to write off R&D in progress related to their acquisition.
- **Acquisition/licensing risk**: Ligand has used acquisitions to expand its business and similar deals may be consummated in the future. It is not possible to know the timing, merits, or terms of such transactions until they are announced. External financing may be required and news of acquisitions may impact the stock price. In addition, the Company has sought partners to complete the development and ultimately commercialize programs in which it has invested. It is possible that future deals will not be completed, or if they are, whether the terms will be comparable to those already finalized. Moreover, corporate strategies change, and that may cause some partnered programs to be terminated rather than completed as expected, which may delay or halt development entirely.
- **Regulatory risk**: Various statutes and regulations address the manufacture, safety, labeling, storage, recordkeeping, and marketing of each product. The lengthy process of seeking approval and the subsequent compliance with applicable statutes and regulations require the expenditure of substantial resources. Any failure to obtain, or any delay in obtaining, regulatory approvals could adversely affect Ligand's business. There is no guarantee that products will be approved by the U.S. Food and Drug Administration (FDA) or international regulatory bodies for marketing.
- **Funding requirements:** It is difficult to predict the Company's future capital requirements. Ligand may need additional financing to continue funding the research and development of its products and to expand its business. There is no guarantee that it can secure the desired future capital or, if sufficient capital is secured, that current shareholders will not suffer significant dilution.

FINANCIAL FORECASTS & VALUATION

Ligand has been operating as a near-virtual company over the past few years, but that might change in the next five years, since we believe profits will soar, largely as Promacta gains acceptance for treating hepatitis C/advanced liver disease patients.

INCOME STATEMENT

Ligand's deep R&D pipeline gives it more shots on goal than any other company of its size, in our view. Not all have the blockbuster potential of Promacta or carfilzomib, but the smaller products in the mix provide diversification and contribute to the overall revenue stream.

Revenue Sources

Nexterone should begin to have a modest impact on Ligand's performance in 2012. Baxter only recently launched the drug, so demand will likely build as the year progresses and healthcare providers learn of the unique properties of this amiodarone formulation. We don't expect Captisol material sales revenue until 2013 as Baxter presumably ordered substantial quantities of Captisol as a result of their recent acquisition of the product from Prism. Nonetheless, Nexterone sales will probably follow a normal growth path, with peak sales of about $175 million reached in its fifth year on the market.

Fablyn should contribute licensing fees of about $2.5 million in the first half of 2012, after generating $1.5 million in the fourth quarter of this year. However, it will likely take time for Chiva to negotiate reimbursement for the drug in Europe where it will launch in 2012 and that will probably limit sales until early 2013. Fablyn will enter a huge market, but it will face stiff competition from other osteoporosis medicines, some that are well established and others that are also newcomers. As a result, we expect penetration of the European market to begin from a low level of about 1% and to increase gradually over 8 years to a peak penetration rate of 10%. Starting in 2014, though, sales of Fablyn may accelerate with its entry into China, Chiva's home country. There, the company may well have a marketing advantage. Our projections are based on Fablyn generating revenues of $10 million in 2016 for Ligand.

Carfilzomib is a wild card in Ligand's portfolio for 2012, in our opinion. While the drug has yielded impressive data in clinical trials and it will receive a "fast track" review by the FDA, its NDA has yet to be accepted by the agency and there is still uncertainty over whether the drug will be approved based on the Phase 2 data. We don't think it would be difficult for the FDA to delay a decision for a few months to get results from a Phase 3 trial that is scheduled to end in mid-summer. (Patients are already able to receive the drug under an expanded access program.) If carfilzomib is approved based on the Phase 2 data, the drug probably will launch by the third quarter. A delay in the approval would push the launch into early 2013, we believe. Ultimately, carfilzomib should do very well, with sales surpassing $1 billion by 2017. Another question is whether Onyx Pharmaceuticals will seek a marketing partner for carfilzomib in Europe, since it has enlisted Ono Pharmaceuticals for Japan. A deal would greatly alter sales estimates for 2012 – 2014. In the meantime, Ligand is supplying clinical-trial quantities of Captisol to Onyx for the two Phase 3 trials that are ongoing and that is the basis of our 2012 estimated contribution from carfilzomib.

Promacta stands apart from all of the other products in Ligand's pipeline. It began to penetrate many of markets around the world in the past 11 months, resulting in a rapid increase in sales – in the September quarter, Promacta generated $35 million of sales, up 25% sequentially and 84% versus the first quarter's $19 million tally. Thus, sales are on track to exceed $100 million for the year, and that would trigger a higher royalty rate on any volume above the $100 million mark. The favorable trend should continue through 2012 as the drug gains acceptance for treating ITP.

Further out, we estimate that ITP accounts for 40%-45% of Promacta revenues in 2016, with a penetration rate of 13% of the addressable market. (We've assumed that there are 750,000 ITP patients in the United States and Europe, of whom 30% stand to benefit from thrombopoietic therapy.) Our projections also reflect an average treatment period of 6 months at price of $23,500.

We believe GlaxoSmithKline will gain regulatory approval of Promacta for treating thrombocytopenia related to hepatitis C and advanced liver disease by early 2013. The patients enrolled in the ENABLE 1 and 2 studies had a life expectancy of only 3 years and they had no therapeutic alternatives. So, even if the top-line "safety signal" from ENABLE 2 is accurate upon further analysis, we believe regulators will approve Promacta for this patient population, since they've approved far more toxic compounds (e.g., cancer chemotherapies) for patients nearing the ends of their lives. In keeping with this approach, we've based our financial projections for Promacta sales on mortality data in the United States and Europe. Combined, there are approximately 100,000 deaths attributable to hepatitis C and/or cirrhosis annually in these two areas. We've assumed that the Promacta-treated patient population will be twice that size, since some patients will probably be treated at an earlier stage of the disease and others will survive after antiviral therapy that they were able to receive, thanks to Promacta. We've further assumed that the average patient receives the drug for 9 months – this reflects differences in treatment regimens based on viral genotypes and an inability of some patients to remain on antiviral therapy despite Promacta. (Genotype 2/3 patients require only 24 weeks of therapy and comprise 35% of the population,[43] while all other genotypes require 72 weeks of the antiviral drug regimen.) Further, we've assumed that penetration of the hepatitis C market starts at 2%-3% and rises to 40% over 10 years. (Note that we have not included other potential indications, including MDS, AML, or chemotherapy-induced thrombocytopenia, in our projections even though preclinical evidence suggests that Promacta will prove safe and efficacious for patients with these conditions.)

The royalty revenue that we estimate Ligand will receive from Promacta is summarized in the following table:

	2011	2012	2013	2014	2015	2016
Projected Promacta Royalties	$ 6,350	$ 10,445	$ 15,500	$ 62,000	$ 108,000	$ 160,000

Operating Costs

Ligand's budget for 2011 calls for investments in R&D of about $10 million and general/administrative expenses to total a little over $16 million. We believe these commitments will not change appreciably next year, since the Company intends to hire only a few more employees and its R&D costs will probably be held in check as investments shift from one program, such as melphalan, to others at an earlier stage of development.

Over the next few years, we have assumed that Ligand acquires additional assets to develop in partnerships with pharmaceutical companies that have marketing operations. Accordingly, R&D expense is projected to rise between 2012 and 2016. We've assumed that a moderate expansion of the corporate infrastructure accompanies the expanded development activities.

Non-Operating Items

As of September 30th, the balance sheet included $10 million borrowed on a bank line of credit and long-term debt of $20.2 million that was assumed to finance the latest acquisition. Interest expense will likely approximate $2.4 million this year and then decline further as Ligand repays the loan over 42 months (starting in January 2012). We've made a small, growing contribution from interest income, but we have not attempted to estimate "Other income/expense" which has been affected greatly by provisions for the corporate liability for contingent value rights. Finally, the income statements were prepared in accordance with financial reporting purposes and as such, they include provisions for income taxes at a 38% rate even though Ligand will probably avoid cash payments for several years – it had federal and state net operating loss carryforwards of $619.3 million as of December 31, 2010, as well as $16.4 million of federal R&D tax credit carryforwards.

[43] McOmish, F, et al. Geographical distribution of hepatitis C genotypes in blood donors: an international collaborative study. J Clin Microbiol 1994; 32(4): 884.

We have made no provisions for equity financing, though we note that the Company recently filed a registration statement for $30 million that may be used to raise capital via debt or equity placements.

ANNUAL INCOME STATEMENTS‡ (Fiscal year ends December 31st.)

	2010	2011	2012	2013	2014	2015	2016
Royalties	$ 7,279	$9,796	$17,000	$ 23,000	$ 73,000	$ 120,000	$ 175,000
Material sales	-	8,182	11,500	18,500	30,000	40,000	50,000
Collaborative R&D/other	16,259	7,322	5,500	5,000	3,000	2,000	2,000
Total Revenues	$ 23,538	$ 25,300	$ 34,000	$ 46,500	$ 106,000	$ 162,000	$ 227,000
Cost of products sold	-	3,851	4,300	6,845	11,100	14,800	18,500
Gross Profit	$ 23,538	$ 21,449	$ 29,700	$ 39,655	$ 94,900	$ 147,200	$ 208,500
Operating expenses							
R&D expense	$ 22,067	$ 10,194	$ 10,000	$ 10,250	$ 12,500	$ 14,000	$ 16,000
G&A expense	12,829	16,297	16,150	16,250	17,000	17,500	18,000
Other	1,052	409	-	-	-	-	-
Total operating costs	35,948	26,900	26,150	26,500	29,500	31,500	34,000
Operating profit/(loss)	$ (12,410)	$ (5,451)	$ 3,550	$ 13,155	$ 65,400	$ 115,700	$ 174,500
Interest income	440	33	310	400	500	1,000	1,250
Interest expense	(58)	(2,497)	(2,400)	(1,800)	(1,000)	(700)	(200)
Other	13,519	(556)					
Pretax profit/(loss)	$ 1,491	$ (8,471)	$ 1,460	$ 11,755	$ 64,900	$ 116,000	$ 175,550
Income taxes	2,617	(313)	(403)	(4,467)	(24,662)	(44,080)	(66,709)
Net profit/(loss) - contin. ops	$ 4,108	$ (8,784)	$ 1,057	$ 7,288	$ 40,238	$ 71,920	$ 108,841
Discontinued/nonrecurring	$ (14,481)	$ 13,782					
Net profit/(loss)	$ (10,373)	$ 4,998	$ 1,057	$ 7,288	$ 40,238	$ 71,920	$ 108,841
Earnings/(loss) per share	$ 0.21	$ (0.45)	$ 0.05	$ 0.36	$ 1.79	$ 3.20	$ 4.78
Discontinued/nonrecurring	$ (0.74)	$ 0.70	$ -	$ -	$ -	$ -	$ -
Shares outstanding	19,623	19,725	19,750	20,000	22,500	22,500	22,750

‡ All data are in thousands, except per-share figures.

Notes:

- Ligand wrote off acquired in-process R&D expense in the amounts of $2.75 million and $2.28 million in 2010 and 2011 respectively. These non-cash charges reflect the return of assets that were originally acquired and then licensed to partners for development. Since these charges are related to the Company's primary business, we have included them as operating costs.

- The Company has booked lease exit and termination costs related to the closure of certain facilities in 2010 in the amount of $16.89 million. This is a non-cash charge with minimal tax impact, which we have combined with gains from discontinued assets in our presentations (annual and quarterly income statements). In addition, Ligand booked a one-time tax benefit of $13.78 million in the first quarter of 2011, which we have treated as a non-recurring event.

- In 2010, Ligand made small adjustments to certain accounts at yearend, so some quarterly line items in the income statements did not add to the total. We have chosen make the adjustments in the fourth quarter presentation so that they do add to the annual figures. As a result, our fourth-quarter numbers differ somewhat from those reported in the press release for the December period results.

QUARTERLY INCOME STATEMENTS (FISCAL YEAR ENDS DECEMBER 31ST.)

All data are in thousands, except for per-share figures.

Estimates are presented in *italics*.

	2010 ‡				2011				2012			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Royalties	$ 1,962	$ 1,601	$ 1,774	$ 1,942	$ 1,993	$ 2,172	$ 2,431	*$ 3,200*	*$ 3,750*	*$ 4,000*	*$ 4,500*	*$ 4,750*
Material sales			-		1,019	2,984	1,679	*2,500*	*2,500*	*2,750*	*3,000*	*3,250*
Collaborative R&D/other	3,996	4,237	6,028	1,998	884	2,307	1,631	*2,500*	*2,000*	*1,500*	*1,000*	*1,000*
Total Revenues	$ 5,958	$ 5,838	$ 7,802	$ 3,940	$ 3,896	$ 7,463	$ 5,741	*$ 8,200*	*$ 8,250*	*$ 8,250*	*$ 8,500*	*$ 9,000*
Cost of products sold	-	-	-		525	1,623	703	*1,000*	*1,000*	*1,000*	*1,100*	*1,200*
Gross Profit	$ 5,958	$ 5,838	$ 7,802	$ 3,940	$ 3,371	$ 5,840	$ 5,038	*$ 7,200*	*$ 7,250*	*$ 7,250*	*$ 7,400*	*$ 7,800*
Operating expenses												
R&D expense	7,362	$ 6,602	$ 4,935	$ 3,168	$ 1,986	$ 3,237	$ 2,471	*$ 2,500*	*$ 2,500*	*$ 2,500*	*$ 2,500*	*$ 2,500*
G&A expense	3,048	3,290	3,074	3,417	4,180	3,855	4,112	*4,150*	*4,000*	*4,000*	*4,050*	*4,100*
Other	(426)	(426)	(426)	2,376	(577)	(442)	1,854	*(426)*	-	-	-	-
Total operating costs	9,984	9,466	7,583	8,961	5,589	6,650	8,437	*6,224*	*6,500*	*6,500*	*6,550*	*6,600*
Operating profit/(loss)	$ (4,026)	$ (3,628)	$ 219	$ (5,021)	$ (2,218)	$ (810)	$ (3,399)	*$ 976*	*$ 750*	*$ 750*	*$ 850*	*$ 1,200*
Interest income	210	118	59	53	30	-	1	*2*	*75*	*75*	*80*	*80*
Interest expense	(18)	(13)	(8)	(19)	(423)	(674)	(700)	*(700)*	*(650)*	*(600)*	*(600)*	*(550)*
Other	1,119	3,858	4,188	4,354	(1,681)	711	214	*200*	-	-	-	-
Pretax profit/(loss)	$ (2,715)	$ 335	$ 4,458	$ (633)	$ (4,292)	$ (773)	$ (3,884)	*$ 478*	*$ 175*	*$ 225*	*$ 330*	*$ 730*
Income taxes	(274)	(625)	(419)	3,935	-	(141)	(22)	*(150)*	*(25)*	*(25)*	*(50)*	*(303)*
Net profit/(loss) - contin ops	*$ (2,989)*	*$ (290)*	*$ 4,039*	*$ 3,302*	*$ (4,292)*	*$ (914)*	*$ (3,906)*	*$ 328*	*$ 150*	*$ 200*	*$ 280*	*$ 427*
Discontinued/nonrecurring	$ 239	$ 7	$ (15,930)	$ 1,203	$ 13,782	$ -	$ -	$ -	$ -	$ -	$ -	$ -
Net profit/(loss)	$ (2,750)	$ (283)	$ (11,891)	$ 4,505	$ 9,490	$ (914)	$ (3,906)	$ 328	$ 150	$ 200	$ 280	$ 427
Earnings/(loss) per share	$ (0.15)	$ (0.01)	$ 0.21	$ 0.17	$ (0.22)	$ (0.05)	$ (0.20)	*$ 0.02*	*$ 0.01*	*$ 0.01*	*$ 0.01*	*$ 0.02*
Discontin'd/nonrecur per sh	$ 0.01	$ 0.00	$ (0.81)	$ 0.06	$ 0.70	$ -	$ -					
Shares outstanding	19,576	19,609	19,630	19,631	19,623	19,650	19,673	*19,675*	*19750*	*19750*	*19800*	*19800*

BALANCE SHEET (FISCAL YEAR ENDS DECEMBER 31ST.)

All data are in thousands.

ASSETS	9/30/2011	12/31/2010
Current Assets		
Cash & equivalents	$ 12,251	$ 22,697
Accounts Receivable	1,719	993
Inventory	1,960	-
Other	2,857	5,295
Co-promotion termination asset	8,030	8,034
Total Current Assets	$ 26,817	$ 37,019
Restricted Cash	1,341	1,341
Property & equipment	678	559
Intangible assets	72,237	12,951
Co-promotion termination asset	20,616	22,851
Other	777	838
Total Assets	$ 122,466	$ 75,559
LIABILITIES		
Current Liabilities		
Accounts payable	$ 23,998	$ 24,177
Deferred gain	426	1,277
Co-promotion termination liability	8,030	8,034
Bank line of credit	10,000	-
Total Current Liabilities	$ 42,454	$ 33,488
Co-promotion termination liability	20,616	22,851
Deferred revenue	1,291	2,546
Long-term debt	20,200	-
Other	27,194	13,179
Total Long-Term Liabilities	$ 69,301	$ 38,576
Com. Stock subject to redemption	8,344	8,344
Shareholders Equity		
Common Stock, par value	$ 21	$ 21
Additional Paid-In Capital	731,899	729,271
Accumulated Deficit	(687,273)	(691,916)
Treasury Stock	(42,280)	(42,225)
Total Shareholders Equity	$ 2,367	$ (4,849)
Total liabilities & equity	$ 122,466	$ 75,559

VALUATION

We've used a simple approach to establishing a 12-month target price for Ligand stock. We applied a P/E multiple of 60 to the estimated share earnings of $0.36 in 2013 to arrive at a future price of $21.60. (The P/E ratio was selected in light of the projected earnings growth, of 79%, between 2014 and 2015.) The future price was discounted back one year using a discount rate of 20%. The final result was a price of $18.00. Accordingly, we have set our 12-month target price of $18 per share.

INVESTMENT CONSIDERATIONS

The investment community has created a buying opportunity by selling Ligand shares before considering the full weight of the data from Promacta studies for the hepatitis C patients with advanced liver disease. Given the dire status of the patients enrolled in the ENABLE 1 and 2 studies, we believe the regulatory agencies will approve Promacta for this additional indication, even if the preliminary ENABLE 2 "safety signal" is unchanged upon further analysis. (But then, it would not be surprising to find that the incidence rate of thromboembolic events is reduced through prudent elimination of a few that are unrelated to the drug therapy – notably those that occurred well after Promacta was cleared from the patients' circulation.)

Our projections are based on a reasonable, but somewhat conservative assessment of Promacta's use, in our opinion. We have included only ITP and hepatitis C patient populations, limited the geographic markets included to the United States and Europe only, and assumed the the addressable market penetration rates will start in the range of 1% – 3% and rise to 13% – 14% by 2016.

If our projections prove accurate, Ligand will have considerable excess cash flow, starting in 2014. Given the Company's business model and its board's decisions over the past five years, we look for more acquisitions and partnering agreements to take place through 2016. That would take advantage of the financial challenges faced by many smaller, yet highly innovative companies in the pharmaceutical and biotechnology industries. Moreover, it would reinvest funds in Ligand's business without altering its operating strategy. However, the Company may still find itself with excess cash, and it is possible that some of those funds will be returned to stockholders in the form of a special dividend and/or share repurchases, in accordance with past decisions by the board of directors. (Indeed, the composition of the board has not changed much over the past four years.)

Over the next 12 months, investors have two events to anticipate that we think will be important valuation inflection points. The first will be more detailed information on the ENABLE 1 and 2 studies via presentations at the 47th Annual Meeting of the European Association for the Study of the Liver that will take place on April 18th – 22nd. The other inflection point will be an announcement that GlaxoSmithKline has submitted a sNDA on Promacta to include hepatitis C patients with advanced liver disease. These should drive the stock to our 12-month target price of $18 per share.

DISCLOSURES

ANALYST(s) CERTIFICATION: The analyst(s) responsible for covering the securities in this report certify that the views expressed in this research report accurately reflect their personal views about Ligand Pharmaceuticals (the "Company") and its securities. The analyst(s) responsible for covering the securities in this report certify that no part of their compensation was, is, or will be directly or indirectly related to the specific recommendation or view contained in this research report.

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Amgen (AMGN)

AstraZeneca (AZN)

Baxter International (BAX)

Bristol-Myers Squibb (BMY)

Cyclacel Pharmaceuticals (CYCC)

GlaxoSmithKline (GSK)

Johnson & Johnson (JNJ)

Onyx Pharmaceuticals (ONXX)

Pfizer (PFE)

Sanofi (SNY)

The Medicines Company (MDCO)

Vertex Pharmaceuticals (VRTX)

PRICE CHART – 2 Year

Source: Nasdaq.com

11/22/2011 – Initiating Coverage: share price: $10.59; rating: BUY; 12-month price target: $18.00.

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